Reaction of gamma-Hydroxy-N-[1-(dimethylcarbamoyl)ethyl]butanamides under the 'Direct Amide Cyclization' Conditions

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Abstract: The preparation of the title compounds was achieved via the 'azirine/oxazolone method' starting from the corresponding gamma-hydroxy acids. Upon subjecting the gamma-hydroxy-N-[1-(dimethylcarbamoyl)- ethyl]butanamides 4 to the so-called 'direct amide cyclization' (DAC) conditions, chlorinated acids 11 or imino lactones 12 were obtained as the sole products instead of the expected cyclodepsipeptides A or their cyclodimers (Scheme 4). Variation of the substituents in 4 did not affect the outcome of the reaction and a mechanism for the formation of both products from the intermediate oxazolone 13 has been proposed. Under the acidic conditions of the DAC, the imino lactones are formed as their HCl salts 12, which, in polar solvents or on silica gel, reacted further to give the chlorinated acids 11. Stabilization of the imino lactones was achieved by increasing the substitution in the five-membered ring, and their structure, in the form of the hydrochlorides, was established independently by X-ray crystallography (Fig. 4). A derivative 15 of the imino lactone 12a was prepared by the reaction with the 2H-azirin-3-amine 10a; its structure was also established by an X-ray crystal-structure determination (Fig. 3). Furthermore, the structures of the omega-chloro acids 11a and 11b were determined by X-ray crystallography (Fig. 2).

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Reaction of γ-Hydroxy-*N*-[1-(dimethylcarbamoyl)ethyl] butanamides under the 'Direct Amide Cyclization' Conditions

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The preparation of the title compounds was achieved *via* the 'azirine/oxazolone method' starting from the corresponding γ-hydroxy acids. Upon subjecting the γ-hydroxy-*N*-[1-(dimethylcarbamoyl)ethyl]butanamides **4** to the 'Direct Amide Cyclization' (DAC) conditions, chlorinated acids **11** or imino lactones **12** were obtained as the sole products instead of the expected cyclodepsipeptides **A** or their cyclodimers (*Scheme 4)*. Variation of the substituents in **4** did not affect the outcome of the reaction and a mechanism for the formation of both products from the intermediate oxazolone **13** has been proposed. Under the acidic conditions of the DAC, the imino lactones are formed as their HCl salts **12**, which, in polar solvents or on silicagel, react further to give the chlorinated acids **11**. Stabilization of the imino lactones was achieved by increasing the substitution in the five membered ring and their structure, in the form of the hydrochlorides, was proven independently by X-ray crystallography (*Fig. 4*). A derivative **15** of the imino lactone **12a** was prepared by the reaction with the 2*H*-azirin-3-amine **10a**; its structure was also established by an X-ray crystal-structure determination (*Fig. 3*). Furthermore, the structures of the ω-chloro acids **11a** and **11b** were determined by X-ray crystallography (*Fig. 2*).

1. Introduction

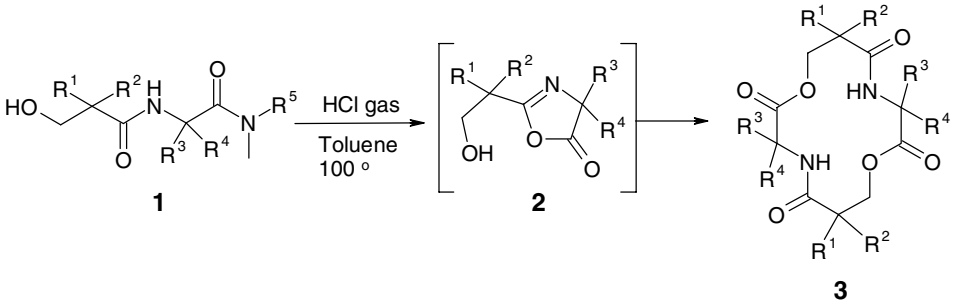
Cyclic depsipeptides, *i.e*. heterodetic cyclopeptides which contain ester (depside) bonds as part of their backbone, have been found in many natural products, and show a wide spectrum of biological activity [1]. They are therefore sought after as promising lead compounds for drug design and discovery. Nature is a rich source of fascinating cyclodepsipeptides, and although the significance of incorporating a depside bond is still not clear, it appears to be essential for biological activity, since all-amide analogues are often inactive [2]. The depside bond is recognized as being more difficult to incorporate into the backbone than the amide bond, although macrolactonizations have been studied extensively [2-6], and is therefore usually pre-formed in the linear precursor prior to the cyclization *via* amide bond formation to give cyclic depsipeptides.

The most-well-known structures in this class of natural products belong to the ion-selective antibiotics, such as valinomycin [7], the closely related enniatin family [8], the actinomycins [9], and others. The reduction in the conformational freedom brought about by cyclization often results in higher receptor binding affinity. Frequently in these cyclic compounds, extra conformational restrictions are also built in, such as D-amino acids, *N*-alkylated-amino acids or α,α-disubstituted amino acids.

A very efficient method for the incorporation of the latter into depsipeptide rings, the so called 'direct amide cyclization' (DAC), has been developed in our research group in recent years. It has been used successfully for the synthesis of 6-, 9-, 12- and 15-membered cyclodepsipeptides from α-hydroxy acids [10-12], as well as larger ring systems from α- and β-hydroxy acids [13-15]. Therefore, we were interested to investigate reactions of dipeptides, containing β-, γ- and δ-hydroxy acids and an α-amino

acid with the aim of synthesizing 7- to 9-membered analogues. As we reported earlier, the cyclization of β-hydroxy acid amides **1**, the linear precursors of the desired 7-membered rings, yielded only cyclodimers **3** by the dimerization process [16][17] (*Scheme 1, Table 1*).

Scheme 1



Monosubstitution at C(α) of the amino acid moiety (R^3=H) did not prevent twinning, although the cyclization was carried out under different conditions [17][2]). If, however, the hydroxy acid moiety in **1** was monosubstituted at C(α), no cyclic depsipeptides were obtained, although the formation of the intermediate 1,3-oxazol-5(4*H*)-one **2** has been monitored by IR spectroscopy. Instead, water elimination occurred, to give derivatives of α,β-unsaturated acid amides.

In the present paper, we describe the results of reactions of the higher homologues of **1** containing γ-hydroxy acids, which were carried out with the aim of obtaining either 8- or 16-membered cyclodepsipeptides.

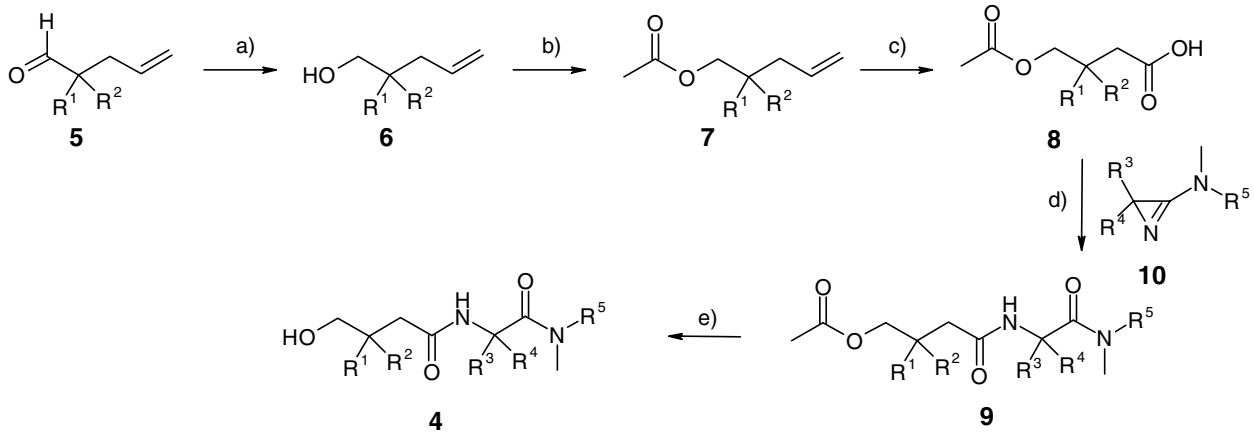
2. Results and Discussion

[2]) The DAC conditions were not applicable in this case because of the sluggish formation of the 1,3-oxazol-5(4*H*)-one intermediate (cf. [18]).

The linear amides **4** were synthesized in five steps from the γ,δ-unsaturated aldehydes **5** (*Scheme 2*). Reduction gave the pentenols **6**, which were acetylated to give **7**[3]). The introduction of the carboxyl group was achieved by oxidative cleavage of the C=C bond of **7,** either with Ru(IV)oxide/$NaIO_4$ [19] or with oxone/acetone [20], although purification proved to be easier in the first case, thus leading to **8** in higher yields. The protection of the hydroxy group prevents the formation of the lactone under these oxidation conditions [21]. The coupling of **8** with the respective amino acid to give **9** was performed by the reaction with 2,2,*N,N*-tetramethyl- or 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirine-3-amine (**10a, 10b**) and *N,N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (**10c**), respectively, at room temperature ('azirine/oxazolone method' [22][23]). Deprotection of the hydroxy group by treatment with LiOH in THF/H_2O led to the linear precursors **4.**

[3]) The need for protection of the hydroxy group arises from the fact that attempts to obtain the desired γ-hydroxy acids from the corresponding easily available lactones (*e.g.* 4,4-dimethyltetrahydropyran-2-one) by alkaline hydrolysis failed. Upon acidification of the sodium salt, spontaneous lactonization occurred and only the starting lactone could be isolated.

Scheme 2



a) $NaBH_4$,MeOH, 0°, 1 h; b) Ac_2O, Pyr, Et_2O, reflux, 1 h; c) $NaIO_4$, Ru(IV)oxide, MeCN,CCl_4, H_2O, r.t.,14 h;
d) **10,** THF, r.t., 24 h; e) LiOH, THF/H_2O, r.t., 2 h.

Table 1. *Synthesized γ-Hydroxyamides* **4** *and Chlorinated Acids* **11**

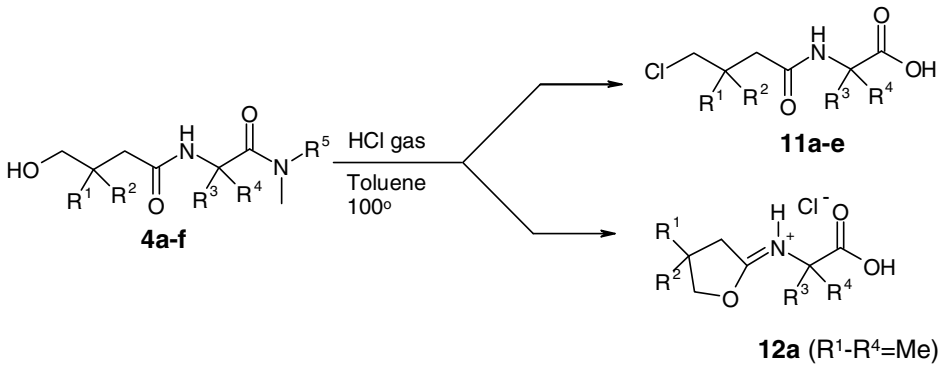
	4a/11a	**4b/11b**	**4c/11c**	**4d/11a**	**4e/11d**	**4f/11e**
R^1	Me	H	Me	Me	H	Me
R^2	Me	H	Me	Me	Ph	Ph
R^3	Me	Me	$-CH_2-CH_2$	Me	Me	Me
R^4	Me	Me	$-CH_2-CH_2$	Me	Me	Me
$R^{5\,a)}$	Me	Me	Me	Ph	Ph	Ph

[a)] R^5 only in **4.**

Unexpectedly, the reactions of **4a-c** (*Table 1*) under the conditions of the 'direct amide cyclization' yielded neither the 8-membered nor the 16-membered cyclodepsipeptides. Instead, after chromatographic workup, the chlorinated acids **11a-c** were isolated as the sole products (*Scheme 3*). If the *N*-methyl-*N*-phenylamide **4d** was used instead of the *N,N*-dimethylamides **4a-c,** the formed product could be isolated after evaporation of the

solvent and washing of the residue with CH_2Cl_2. The isolated product was identified as the imino lactone hydrochloride **12a** (*Scheme 3*).

Scheme 3



At first it seems that R^5 is determining the product of the reaction. Indeed, it has been shown that in some DAC reactions *N*,*N*-dimethyl- and *N*-methyl-*N*-phenyl amides behave quite differently [15]. Therefore, the cyclization of **4e** and **4f** was attempted under DAC conditions. Surprisingly, in both cases the product was not the imino lactone of type **12,** but the chlorinated acid of type **11**. Therefore, the presence of the PhN residue is not the reason for the different behavior of **4d** under DAC conditions.

The explanation lies in the purification process. Since *N*-methylaniline hydrochloride is soluble in CH_2Cl_2 [16][17] and the products of the reaction are not, the crude residue in the case of **4d** was just washed with CH_2Cl_2, and thus the imino lactone was isolated as its hydrochloride **12a** in pure form. On the other hand, $Me_2NH.HCl$ is insoluble in CH_2Cl_2, so that chromatographic workup was necessary in the case of **4a-c**, which led to the formation of the corresponding chloro acids **11**. In the case of **4e,f**, due to the presence of the Ph substituent in the hydroxy acid moiety, the product of the reaction was soluble in CH_2Cl_2 and no precipitate was formed. For this reason, chromatographic purification was required which yielded chlorinated acids **11** as the sole product (*Scheme 3*).

It is worth mentioning, that the ^{1}H-NMR spectrum of **12a** in (D_6)DMSO changes with time. After just half an hour at room temperature, the appearance of signals at 1.00, 1.31, 2.09, 3.59 and 8.05 ppm was observed, which grew stronger with time, while the signals at 1.15, 1.56, 3.13 and 4.56 ppm diminish (*Fig. 1)*.

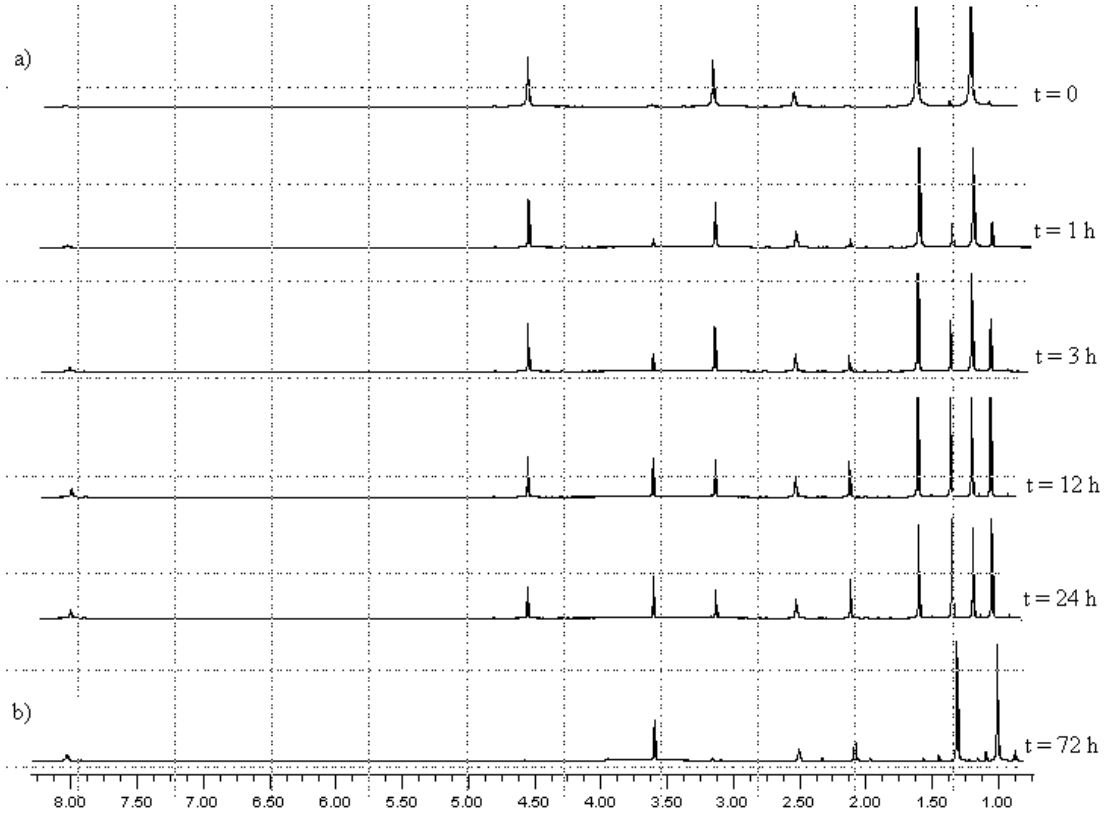
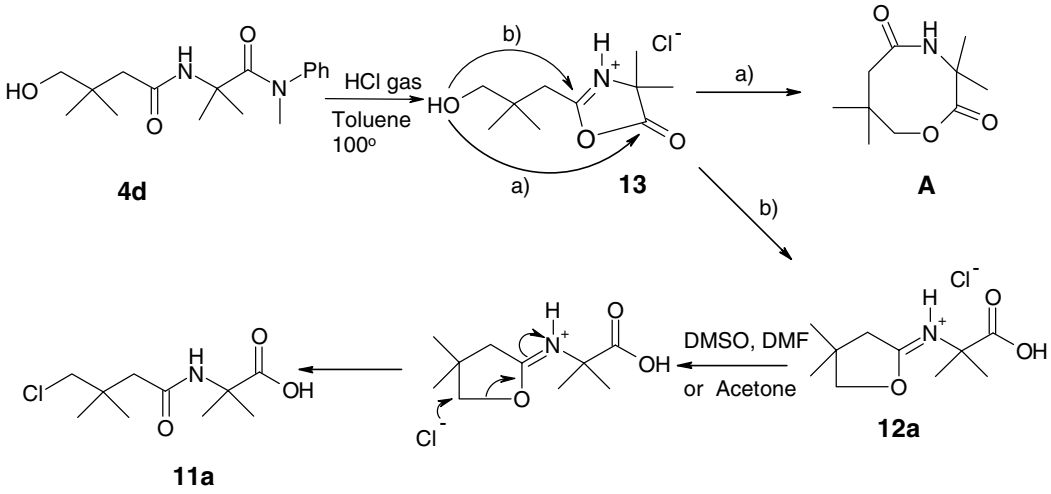


Fig. 1. *Dynamic ^{1}H-NMR spectrum of* **12a** *in (D_6)DMSO: a) Spectrum of* **12a***, b) Spectrum of* **11a**

The new signals were sharp and well defined, indicating the formation of a single compound, rather than decomposition. After *ca.* 12 h at room temperature, the ratio of both compounds was roughly 1:1, while after 3 d only traces of the starting compound **12a** could be observed. The spectrum of the newly formed substance coincides with the spectrum of **11a**. The same process was also observable in the ^{13}C NMR spectrum, the isomerization proceeding in a variety of polar solvents such as DMF and acetone. In the

latter, the ratio between **12a** and **11a** reached 1:1 in about a week and then remained constant. Flash chromatography of a mixture of **11a** and **12a** allowed the isolation of analytical amounts of **12a**. Finally, the instability of **12a** in solution was proven in a control experiment in which a mixture of **12a** and **11a** in CH_2Cl_2 containing 10% of MeOH was stirred at room temperature. After 14 h, only the chlorinated acid **11a** was isolated. Apparently, under the DAC reaction conditions, the initially formed product is the imino lactone hydrochloride **12a**, which, in polar solvents, undergoes an isomerization to give **11a** (*Scheme 4*).

Scheme 4



A reaction mechanism for the formation of **11a** and **12a** is shown in *Scheme 4*. Treatment of **4d** with HCl gas leads to the corresponding 1,3-oxazol-5(4*H*)-one **13**. When no external nucleophiles are present, the OH group acts as a nucleophile and attacks one of the two electrophilic centres in the ring. If the attack occurs at the C=O group (pathway a), the 8-membered cyclodepsipeptide **A** would be formed. On the other hand, the OH attack at the C=N group (pathway b), would lead to the opening of the oxazolone ring yielding the imino lactone hydrochloride **12a**. The latter can be isolated if no chromatographic workup is necessary. In a polar solvent, the chloride ion apparently

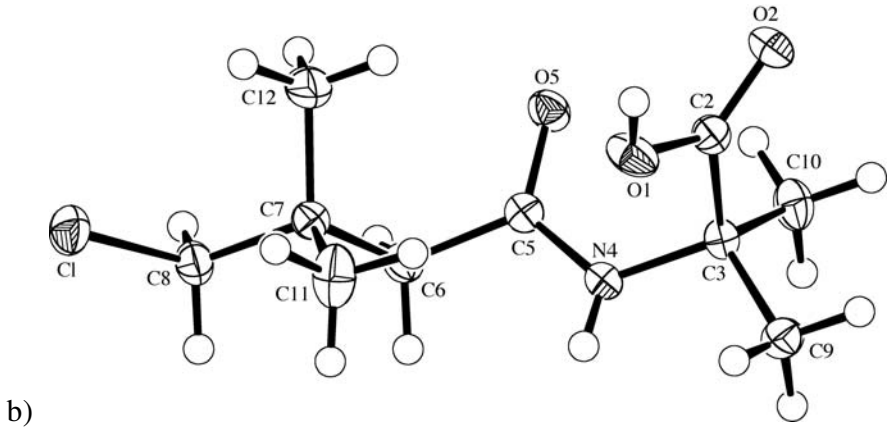
attacks the methylene group adjacent to the O-atom, which leads to the open chain *ω*-chloro acid **11a**[4]).

Due to its instability in solution, no crystals of **12a** suitable for an X-ray crystal structure determination could be obtained, but the structures of the chlorinated acids **11a** and **11b** were confirmed by X-ray crystallography (*Fig. 2*)[5]).

[4]) We expect that in the presence of a better nucleophile a competition with the attack of Cl^- should be possible, which would lead to a mixture of products, but all reactions in the presence of CsI, Bu_4NI and PhSNa, respectively, led to the formation of **11** exclusively.

[5]) The structure of **11c** has also been proven by an X-ray crystal-structure determination. The quality of the crystals and, subsequently, the results of the structure determination were poor, although unambiguous. The results are not reported here, but have been deposited at the CCDC (see footnote 6).

a)



b)

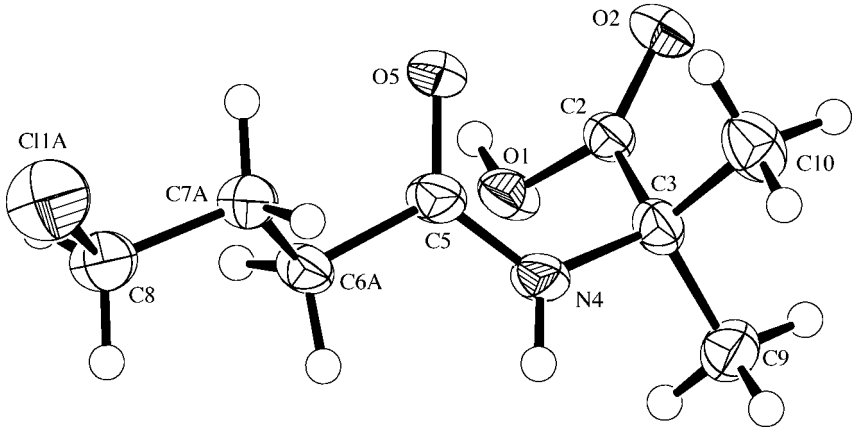


Fig. 2. ORTEP *Plots* [24] *of the molecular structures of a)* **11a** *and b) one of the disordered conformations of one of the two symmetry-independent molecules of* **11b** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

The OH group in **11a** forms an intermolecular H-bond with the amide O-atom of a neighboring molecule, thereby linking the molecules into extended chains which run parallel to the [0 1 0] direction and can be described by a graph set motif [25] of C(7). The amide group forms an intermolecular H-bond with the carboxylate carbonyl O-atom of a different neighboring molecule, thus also linking the molecules into extended chains. These chains run parallel to the [1 0 0] direction and can be described by a graph set

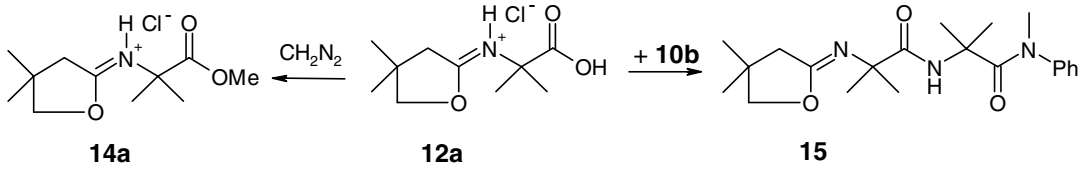
motif of C(5). The combination of both interactions generates a two-dimensional network, which lies parallel to the (0 0 1) plane.

In the case of **11b,** there are two symmetry-independent molecules in the asymmetric unit. The most significant difference between the independent molecules is in the orientation of the Cl-atom. Furthermore, each of the two symmetry-independent molecules is disordered over the Cl-$(CH_2)_3$- section of the molecule. Two positions were defined for these atoms in each molecule, except for the Cl-substituted C-atom, which is common to both conformations. The major conformation is present in approximately 65% and 80% of molecules A and B, respectively. Except for the orientations of the Cl-atoms, the major conformation of molecule A is almost identical to that of the minor conformation of molecule B and *vice-versa*. The OH group of each molecule in **11b** forms an intermolecular hydrogen bond with the amide O-atom of an adjacent molecule of the same type. These interactions link the molecules into infinite extended chains composed entirely of molecules of type A or entirely of type B. These chains run in the [1 0 1] direction and can be described by a graph set motif of C(7). The amide group of each molecule forms an intermolecular H-bond with the carbonyl O-atom of the carboxyl group of an adjacent symmetry-independent molecule. These interactions link the molecules into extended ···A···B···A···B··· chains which run in the [0 0 1] direction and can be described by a binary graph set motif of $C_2^2(10)$. The combination of all H-bonding interactions links the molecules into extended two-dimensional networks which lie parallel to the (0 1 0) plane.

In order to isolate the crucial intermediate **12a**, extraction with aq. Na_2CO_3 solution [26] and deprotection by treatment with polyvinylpyridine were attempted, but neither procedure gave satisfying results. Although esterification of **12a** with CH_2N_2 yielded the

corresponding crude methyl ester hydrochloride **14a** (*Scheme 5*), the product was also not stable in polar solvents and isomerized partially to the corresponding chloro ester.

Scheme 5



14a **12a** **15**

Finally, the reaction of **12a** with 2*H*-azirin-3-amine **10b** yielded the diamide **15**, which was stable in solution and whose structure was confirmed by X-ray crystallography (*Fig. 3*). This is the first direct proof of the tetrahydrofuran-2-imine structure.

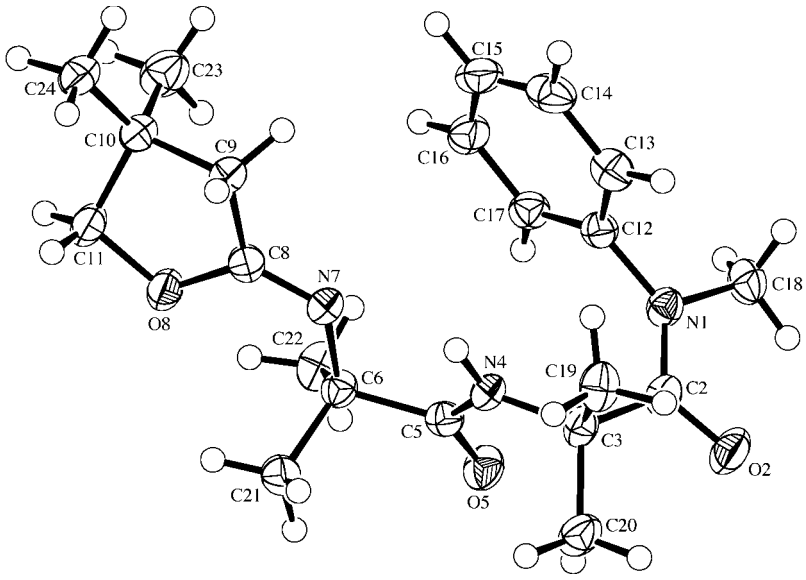


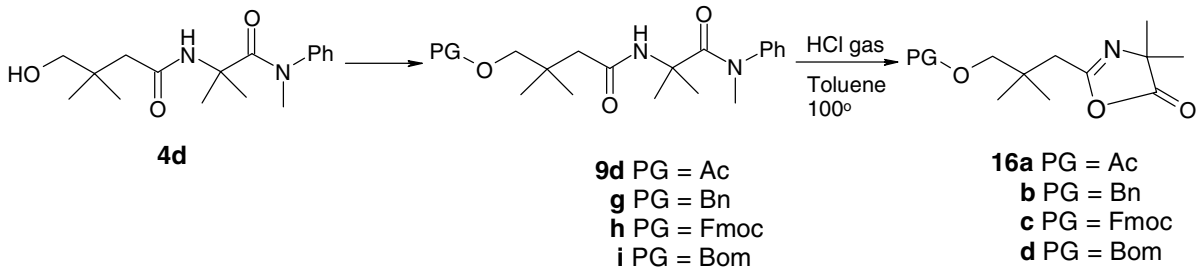
Fig. 3. ORTEP *Plot* [24] *of the molecular structure of* **15** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

The central amide group (N(4)H) of **15** has a weak intramolecular H-bonding interaction with the imine N-atom (N(7)), which results in a five-membered loop that can be described by a graph set motif [25] of S(5).

When the hydroxy-protected amide **9d** was subjected to the DAC conditions, the corresponding protected 1,3-oxazol-5(4*H*)-one **16a** (*Scheme 6)* was isolated in good yield, which indicated that an oxazolone, *i.e.* **13** in *Scheme 4,* is most probably the first intermediate from which the imino lactones **12** and the chloro acids **11** are formed. Therefore, we decided to prepare **9g-i** with different protecting groups, which could potentially allow the deprotection and isolation of the oxazolone with a free hydroxy group as a precursor for the cyclization to give **A**.

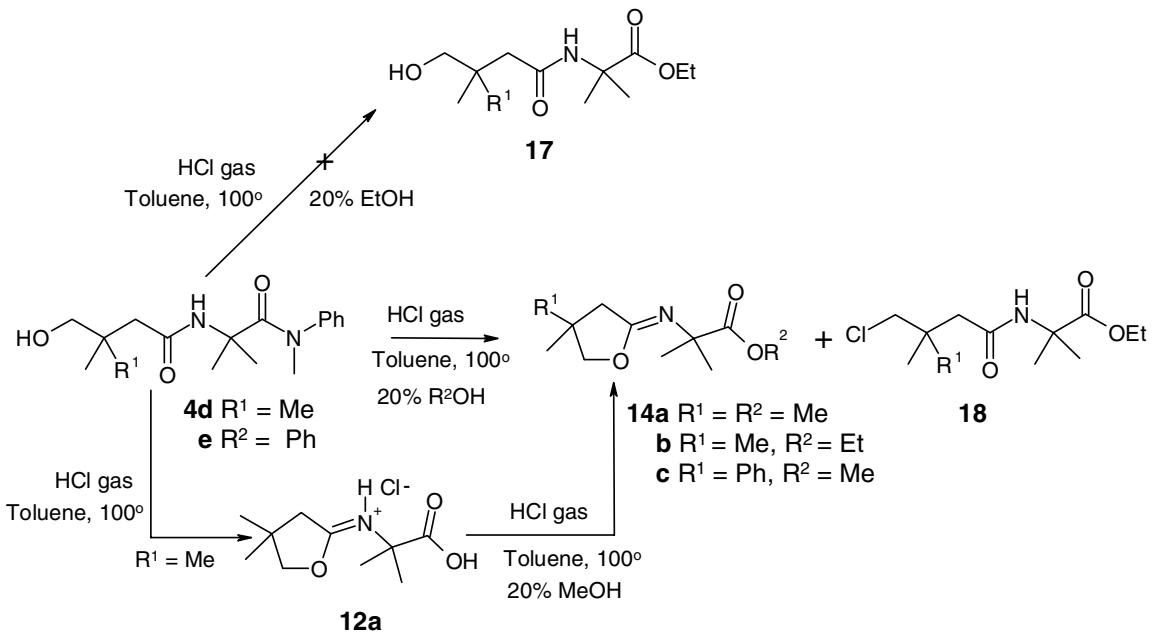
We planned to prepare **9g-i** analogously to **9d** (*Scheme 2).* The benzyl, (benzyloxy)methyl (Bom) and Fmoc protecting group could be introduced before the oxidative clevage of the double bond and yield the protected acids of type **8,** which could then be reacted with 2*H*-azirin-3-amine **10b** to give the protected diamides **9**. Because of the instability of the protecting group under the oxidation conditions, direct protection of the hydroxy amide **4d** was preferred (*Scheme 6*). Unfortunately, the deprotection failed in all cases.

Scheme 6



Since the DAC method failed to give cyclic depsipeptides, we attempted to synthesize the hydroxy esters of type **17** from amides **4** and to subject them to the NaH cyclization procedure, described earlier [16][17]. Unexpectedly, treatment of **4d** and **4e** with HCl gas in toluene containing 20% EtOH as an external nucleophile did not yield the desired esters **17,** but gave as the main products the imino lactone esters **14** in moderate yields together with the corresponding ω-chloro esters **18** (*Scheme 7*).

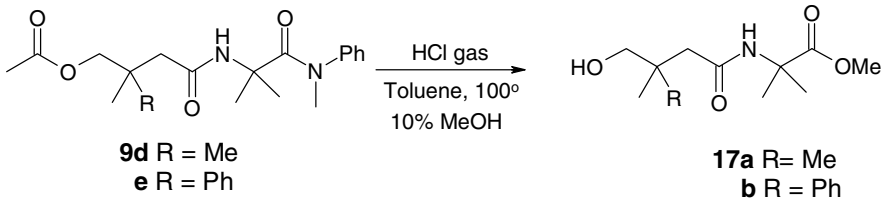
Scheme 7



Further experiments with **4d** in the presence of MeOH showed that the ester could also be formed directly from the imino lactone **12a,** either under DAC conditions or by treatment with CH_2N_2 (*Schemes 5* and *7).*

If instead of the hydroxy amides **4,** the protected alcohols **9d** or **9f** were subjected to the DAC conditions in the presence of MeOH, the unprotected linear esters **17** were formed (*Scheme 8*). We believe that again oxazolones are the intermediates and since the OH group in **9** is protected, it is to be expected that protected oxazolones of type **16** (*Scheme 6*) are the intermediates. Nucleophilic addition of MeOH to the oxazolone, followed by ring opening, leads to the ester group in **17**. The deacetylation could be explained by trans-esterification, *via* formation of AcOMe, which is a common reaction under acidic conditions.

Scheme 8

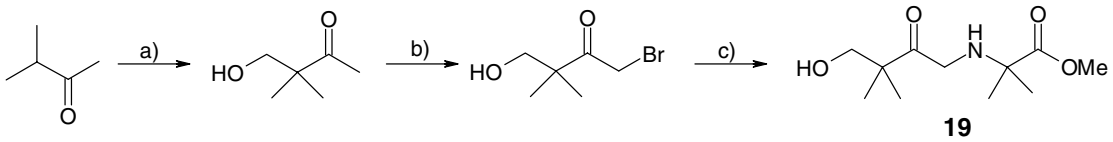


9d R = Me
e R = Ph

17a R= Me
b R = Ph

The esters **17** were subjected to the conditions of the NaH-catalyzed cyclization, *i.e.* they were treated with NaH in toluene at 80° [16][27], but no cyclic products were obtained. As in previous studies [16][17], the rigidity of the amide bond was suggested as the reason for the failure. Therefore, the aminoketone **19** was synthesized, as depicted in *Scheme 9,* and subjected to the same reaction conditions. Again, no cyclic products could be identified in the mixture.

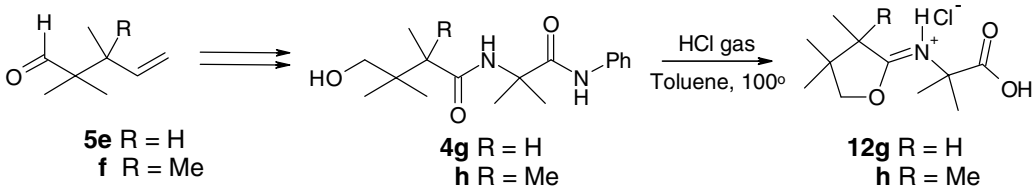
Scheme 9



a) HCHO, NaOH, 72%; b) Br_2, 88%; c) Ethyl 2-amino-2-methylpropanoate hydrochloride, Et_3N, 39%

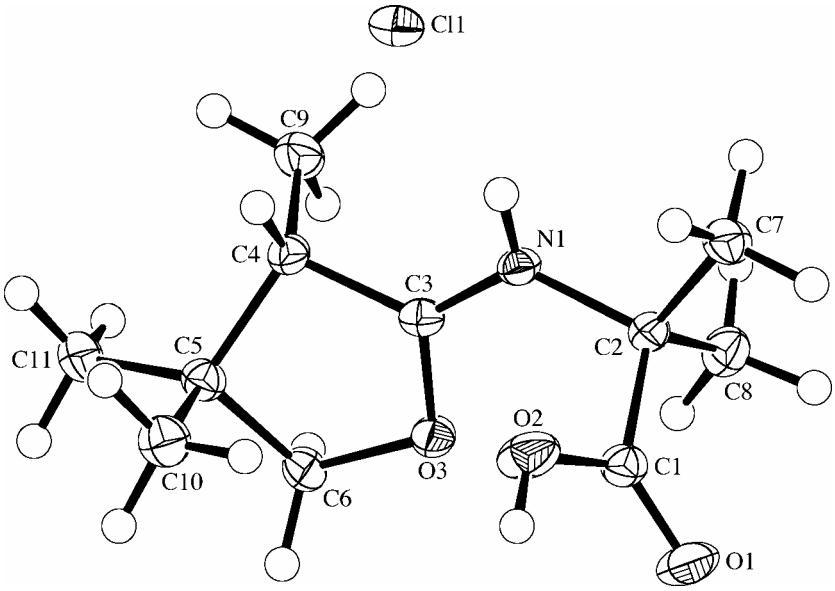
If indeed the formation of the cyclic products **12** and **14** occurs *via* the attack of the OH group at the imminium C-atom of the oxazolone **12** (see *Scheme 4*, path b), α-substitution in the hydroxy diamide **4** might present sufficient steric hindrance in order to direct the nucleophilic attack onto the ester group (*Scheme 4*, path a). Therefore, the amides **4g** and **4h** were prepared analogously to *Scheme 2*. Treatment of amides **4g** and **4h** with HCl gas in toluene at 100° (DAC conditions) yielded imino lactones as sole products (*Scheme 10).*

Scheme 10



Unlike their analogues **12a-c,** compounds **12g,h** are stable in solution. The higher substitution of the ring apparently stabilizes it, *i.e.* the *gem*-dimethyl effect, (*Thorpe-Ingold* effect [28]) makes the ring opening thermodynamically unfavorable. Thanks to their stability in solution, crystals suitable for an X-ray crystal structure determination could be grown for both hydrochlorides **12g** and **12h** (*Fig. 4*).

a)



b)

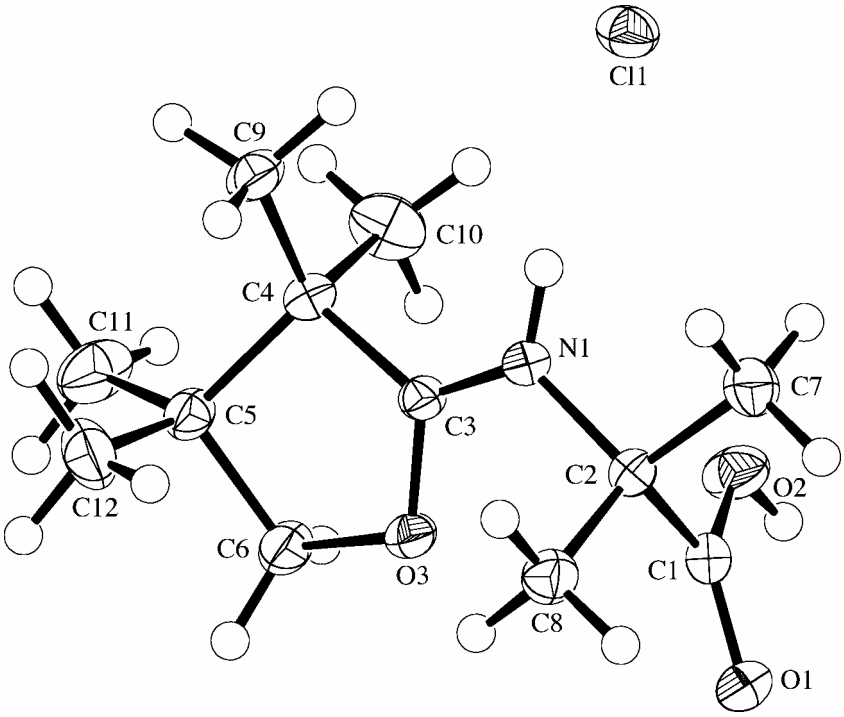


Fig. 4. ORTEP *Plots* [24] *of the molecular structures of a)* **12g** *and b)* **12h** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

Since the space group of **12g** is centrosymmetric, the compound in the crystal is racemic. The OH group forms a H-bond with a neighboring chloride ion, while the imminium group forms a H-bond with a different chloride ion. Thus, each chloride ion accepts two H-bonds. These interactions link two cations and two anions in a cyclic manner into a tetrameric unit and can be described by a graph set motif [25] of $R_4^2(14)$.

Similar H-bonding interactions occur in **12h,** but this time the interactions link the ions into extended chains, which run parallel to the [1 0 0] direction and can be described by a graph set motif of $C_2^1(7)$.

Conclusions

When γ-hydroxy diamides **4** were subjected to the DAC reaction conditions, neither the 8-membered nor the 16 membered depsipeptides were formed. Depending on the work-up procedure, either the chlorinated acids **11** or the imino lactone hydrochlorides **12** with a carboxyl group were obtained as the sole products in good yields. Both products are formed *via* the intermediate oxazolones by an attack of the OH group at the iminium C-atom, instead of at the carbonyl group of the oxazolone (*Scheme 4*). This attack leads to the five-membered ring, instead of the desired eight-membered ring. The former are obviously more stable than the latter.

Compounds **12**, with α-H atoms next to the carbonyl group, are unstable in solution and isomerize to the corresponding ω-chloro acids **11**. Increased substitution of the imino lactone stabilizes the five membered ring and prevents isomerization. A few other cyclization methods were also tried, but they all failed to give cyclic depsipeptides.

Experimental Part

1. *General*. See [16].

2. *Starting Materials.* 2,2,*N*,*N*-Tetramethyl-2*H*-azirin-3-amine (**10a**), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**10b**), and *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (**10c**) were prepared according to standard procedures (*cf.* [16] and refs. cited therein). 2,2-Dimethylpent-4-enal (**5a**) was prepared from isobutyraldehyde according to *Noack et al.* [29], 2-phenylpent-4-en-1-ol (**6c**) was obtained from 2-phenylpropanal by following the method of *Iqbal et al.* [30], and 2-methyl-2-phenylpent-4-enal (**5d**) was synthesized from 2-phenylpropanal analogously to **5a**. All spectra were in accordance with literature data [31]. 2,2,3-Trimethylpent-4-enal (**5e)** and 2,2,3,3-tetramethylpent-4-enal (**5f**) were prepared according to *Brannock et al.* [32] from crotyl bromide and 1-bromo-3-methylbut-2-ene, respectively. 1-Bromo-4-hydroxy-3,3-dimethylbutan-2-one (**23)** was synthesized according to *Mihelcic et al.* [33]. All other products used were commercially available.

3. *Preparation of Pent-4-enyl Acetates. General Procedure 1 (GP 1).* To a soln. of the corresponding pent-4-enal **5** (5 mmol) in MeOH (20 ml) at 0^{o}, $NaBH_4$ (760 mg, 20 mmol) was added in small portions within 20 min, then the mixture was allowed to warm to r.t. and was stirred for a total of 1 h. The solvent was evaporated *i.v.* and the residue dissolved in H_2O. Extraction with Et_2O (5 × 30 ml), drying ($MgSO_4$) and evaporation *i.v.* yielded the pent-4-en-1-ols **6**, which were acetylated without further purification. For this purpose, **6** (5 mmol) was dissolved in Et_2O (50 ml) and pyridine (0.81 ml, 10 mmol) was added. The mixture was heated to reflux and a soln. of Ac_2O (0.41 ml, 5.5 mmol) in Et_2O

(10 ml) was added dropwise within 20 min. The mixture was stirred under reflux for another 1.5 h, cooled, the salt was filtered off, the org. layer washed with 10% aq. $CuSO_4$ soln. and brine, dried ($MgSO_4$), evaporated *i.v.* and purified by column chromatography (CC, SiO_2) to yield the desired pent-4-enyl acetates **7**.

3.1. *2,2-Dimethylpent-4-enyl Acetate* (**7a**). According to *GP 1* from 2,2-dimethylpent-4-enal (**5a**, 560 mg, 5 mmol), CC (hexane/Et_2O 10:1). Yield: 593 mg, 79% of **7a** as a colorless oil. All spectra were in accordance with literature data [34].

3.2. *2-Phenylpent-4-enyl Acetate* (**7c**). To a soln. of 2-phenylpent-4-en-1-ol (**6c**, 5 mmol, 810 mg) in Et_2O (50 ml), pyridine (0.81 ml, 10 mmol) was added, the mixture was heated to reflux and then a soln. of Ac_2O (0.71 ml, 5.5 mmol) in Et_2O (10ml) was added dropwise over 20 min. The reaction was stirred under reflux for another 1.5 h, cooled, the pyridinium acetate filtered off, the org. layer washed with 10% aq. $CuSO_4$ soln. and brine, dried ($MgSO_4$), evaporated *i.v.* and purified by CC (hexane/Et_2O 15:1) to yield 860 mg (84%) of **7c**. Colorless oil. ^{1}H-NMR: 1.98 (*s,* MeCO); 2.24-2.41 (*m,* CH_2); 2.91-3.06 (*m,* PhC*H*); 4.11-4.26 (*m,* CH_2O); 4.92-5.09 (*m,* C*H*$_2$=CH); 5.62-5.83 (*m,* CH_2=C*H*); 7.12-7.39 (*m,* 5 arom. H). ^{13}C-NMR: 20.8 (*q*, Me); 36.8 (*t*, CH_2); 44.4 (*d*, CH); 67.6 (*t*, CH_2O); 116.6 (*t*, *C*H$_2$=CH); 126.7, 127.4, 128.3 (3*d*, 5 arom. CH), 135.6 (*d*, CH_2=*C*H); 141.3 (*s,* arom. C); 170.8 (*s,* C=O). ESI-MS: 205 (100, $[M + H]^+$).

3.3. *2-Methyl-2-phenylpent-4-enyl Acetate* (**7d**). According to *GP 1* from 2-methyl-2-phenylpent-4-enal (**5d**, 870 mg, 5 mmol), CC (hexane/Et_2O 20:1). Yield: 785 mg (72%) of **7d**. Colorless oil. IR: 3075*s,* 2962v*s,* 2860v*s,* 1745v*s,* 1636*s,* 1482*s,* 1432*s,* 1386*s,* 1334*s,* 1188*s,* 1076*s,* 1029*s,* 912*m*. ^{1}H-NMR: 1.35 (*s,* Me); 2.05 (*s,* MeCO); 2.31-2.59 (*m,* CH_2); 4.13-4.28 (*m,* CH_2O); 4.87-5.11 (*m,* C*H*$_2$=CH); 5.45-5.59 (*m,* CH_2=C*H*); 7.14-7.44 (*m,* 5 arom. H). ^{13}C-NMR: 20.7, 22.5 (2*q*, 2 Me); 41.0 (*s,* C); 43.4 (*t*, CH_2); 71.4 (*t*,

CH_2O); 117.8 (*t*, *C*H_2=CH); 126.1, 127.7, 128.1 (3*d*, 5 arom. CH); 133.3 (*d*, CH_2=*C*H); 144.3 (*s,* arom. C); 170.9 (*s,* C=O). ESI-MS: 219 (100, $[M + H]^+$).

3.4. *2,2,3-Trimethylpent-4-enyl Acetate* (**7e**). According to *GP 1*, from 2,2,3-trimethylpent-4-enal (**5e,** 5 mmol, 630 mg), CC (hexane/Et_2O 10:1). Yield: 604 mg (71%) of **7e**. Colorless oil. IR: 3077*w,* 2973v*s,* 2879*s,* 1744v*s,* 1637*m,* 1473*m,* 1377*s,* 1036*s,* 914*m*. ^{1}H-NMR: 0.86, 0.90 (2*s,* Me_2C); 0.98 (*d*, *J* = 4.5, Me); 1.98 (*s,* MeCO); 2.11-2,23 (*m,* MeC*H*); 3.36 (*s,* CH_2O); 4.90-5.04 (*m,* CH_2=CH); 5.74-5.92 (*m,* CH_2=C*H*). ^{13}C-NMR: 14.6, 20.8, 21.6 (3*q*, Me, *Me*$_2$C, *Me*CO); 36.5 (*s,* Me_2C), 40.9 (*d*, Me*C*H); 70.4 (*t*, CH_2O); 114.1 (*t*, *C*H_2=CH); 141.5 (*d*, CH_2=*C*H); 171.8 (*s,* C=O). ESI-MS: 193 (100, $[M + H]^+$).

3.5. *2,2,3,3-Tetramethylpent-4-enyl Acetate* (**7f**). According to *GP 1*, from 2,2,3,3-tetramethylpent-4-enal (**5f,** 5 mmol, 700 mg), CC (hexane/Et_2O 10:1). Yield: 717 mg (78%) of **7f**. Colorless oil. IR: 3072*m,* 2964v*s,* 2909*s,* 1746v*s,* 1635*m,* 1473*m,* 1414*m,* 1380*s,* 1315*s,* 1040*s,* 913*s*. ^{1}H-NMR: 0.88, 0.99 (2*s,* 2 Me_2C); 2.02 (*s,* MeCO); 3.90 (*s,* CH_2O); 4.89-5.00 (*m,* CH_2=CH); 5.87-5.96 (*m,* CH_2=C*H*). ^{13}C-NMR: 20.5 (*q*, *Me*$_2$C); 21.0 (q, *Me*CO); 22.6 (*q*, *Me*$_2$C); 38.3, 40.8 (2*s,* 2 Me_2C); 70.6 (*t*, CH_2O); 112.0 (*t*, *C*H_2=CH); 145.3 (*d*, CH_2=*C*H); 171.3 (*s,* C=O). ESI-MS: 207 (100, $[M + H]^+$).

4. *4-Acetoxybutanoic Acids* **8.** *General Procedure 2 (GP 2)*. To a soln. of pent-4-enyl acetates **7** (5 mmol) in MeCN/CCl_4/H_2O 2:2:3 (70 ml), $NaIO_4$ (2.28 g, 20 mmol) was added under stirring. After 10 min, a catalytic amount of $RuO_2.H_2O$ was added and the mixture stirred vigorously at r.t. for 4-12 h. Filtration of the white residue over celite, washing with CH_2Cl_2, extraction of the collected mother liquor with CH_2Cl_2, drying ($MgSO_4$), evaporation *i.v.* and purification by CC yielded **8** as colorless oils.

4.1. *4-Acetoxy-3,3-dimethylbutanoic Acid* (**8a**). According to *GP 2* from **7a** (5 mmol, 780 mg), 6 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 625mg (73%) of **8a.** Colorless oil. IR: 3284 *s* (br), 2969*s,* 1739v*s,* 1709v*s,* 1475*w,* 1379*s,* 1243*s,* 1041*s,* 926*w.* ^{1}H-NMR: 0.98 (*s,* Me_2C); 1.98 (*s,* MeCO); 2.28 (*s,* CH_2); 3.88 (*s,* CH_2O); 9.83 (br. *s,* COOH). ^{13}C-NMR: 20.6 (*q*, Me); 24.9 (*q*, *Me*$_2$C); 33.5 (*s,* Me$_2$*C*), 42.8 (*t*, CH_2); 71.6 (*t*, CH_2O); 171.1 (*s,* C=O); 177.7 (*s,* COOH). ESI-MS: 197 (100, $[M + Na]^+$).

4.2. *4-Acetoxy-3-phenylbutanoic Acid* (**8c**). According to *GP 2*, **7c** (5 mmol, 1.020 g), 4 h, CC (CH_2Cl_2/acetone 20:1). Yield: 678 mg (61%) of **8c**. Colorless oil. ^{1}H-NMR: 1.99 (*s,* MeCO); 2.61-2.88 (*m,* CH_2); 3.42-3.58 (*m,* PhC*H*); 4.09-4.36 (*m,* CH_2O); 7.13-7.38 (*m,* 5 arom. H.); 10.63 (br. *s,* COOH). ^{13}C-NMR: 20.6 (*q*, *Me*CO); 37.1 (*t*, CH_2), 40.7 (*d*, CH); 67.3 (*t*, CH_2O); 127.2, 127.5, 128.6 (3*d*, 5 arom. CH); 139.8 (*s,* arom. C); 170.7 (*s,* C=O); 177.3 (*s,* COOH). ESI-MS: 245 (100, $[M + Na]^+$).

4.3. *4-Acetoxy-3-methyl-3-phenylbutanoic Acid* (**8d**). According to *GP 2* from **7d** (5 mmol, 1090 mg), 6 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 861mg (73%) of **8d.** Colorless oil. ^{1}H-NMR: 1.31 (*s,* Me); 2.01 (*s,* MeCO); 2.28-2.36 (*m,* CH_2); 4.18-4.45 (*m,* CH_2O); 7.08-7.38 (*m,* 5 arom. H). ^{13}C-NMR: 20.9 (*q*, *Me*CO); 26.6 (*q,* Me); 31.1 (*s,* Me$_2$*C*); 45.7 (*d*, CH); 69.3 (*t*, CH_2O); 127.3, 127.6, 128.9 (3*d*, 5 arom. CH); 141.2 (*s,* arom. C); 171.4 (*s,* C=O); 176.1 (*s,* COOH). ESI-MS: 259 (100, $[M + Na]^+$).

4.4. *4-Acetoxy-2,3,3-trimethylbutanoic Acid* (**8e**). According to *GP 2* from **7e** (5 mmol, 850 mg), 6 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 771mg (82%) of **8e**. Colorless oil. IR: 3466 br. *s,* 2976*s,* 1738v*s,* 1710v*s,* 1467*w,* 1390*s,* 1245*s,* 1041*s,* 925*w***.** ^{1}H-NMR: 0.95, 0.99 (2*s,* Me_2C); 1.18 (*d, J* = 4.7, *Me*CH); 2.00 (*s,* MeCO); 2.48 (*q, J* = 4.7, MeC*H*); 3.89 (*s,* CH_2O); 10.11 (br. *s,* COOH). ^{13}C-NMR: 15.6, 20.6 (2*q*, 2 Me); 21.8, 22.1 (2*q*,

Me$_2$C); 38.7 (*s,* Me$_2$*C*); 45.1 (*d,* CH); 70.8 (*t*, CH_2O); 171.0 (*s,* C=O); 181.3 (*s,* COOH). ESI-MS: 211 (100, $[M + Na]^+$).

4.5. *4-Acetoxy-2,2,3,3-tetramethylbutanoic Acid* (**8f**). According to *GP 2* from **7f** (5 mmol, 920 mg), 4 h, CC (CH_2Cl_2/MeOH 20:1). Yield: 524 mg (52%) of **8f**. IR: 3290*s* (br)*,* 2972*s,* 1743v*s,* 1477*m,* 1377*m,* 1248*s,* 1214*w,* 1040*s,* 1021*w,* 926*w*. ^{1}H-NMR: 0.99, 1.19 (2*s,* 2 Me$_2$C); 2.03 (*s,* MeCO); 3.99 (*s,* CH_2O); 9.63 (br. *s,* COOH). ^{13}C-NMR: 20.6 (*q*, MeCO); 21.1, 21.4 (2*s,* 2 *Me*$_2$C); 38.3, 46.9 (2*s,* 2 Me$_2$*C*); 70.1 (*t*, CH_2O); 171.1 (*s,* C=O); 183.3 (*s,* COOH). CI-MS: 203 (38, $[M + H]^+$), 143 (100, $[M - MeCO]^+$).

5. *Coupling of* **8** *with 2*H-*Azirin-3-amines* **10.** *General Procedure 3 (GP 3).* Acids **8** were taken up in dry THF (20 ml) and the corresponding aminoazirine **10** was added dropwise. The mixture was stirred overnight at r.t., the solvent evaporated *i.v.* and the residue purified by CC to yield acetoxy diamides **9**.

5.1. *3-[1-Methyl-1-(*N,N-*dimethylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl Acetate* (**9a**). According to *GP 3* from **8a** (348 mg, 2 mmol) in dry THF (20 ml) and **10a** (235 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 30:1). Yield: 509 mg (89%) of **9a**. White powder. M.p. 99.1-99.2°. ^{1}H-NMR: 0.98, 1.52 (2*s,* 2 Me$_2$C); 2.05 (*s,* MeCO); 2.10 (*s,* CH_2); 3.08 (br. *s,* Me$_2$N); 3.98 (*s,* CH_2O); 7.12 (*s,* NH). ^{13}C-NMR: 20.9 (*q*, *Me*CO); 24.5, 24.7 (2*q*, 2 *Me*$_2$C); 34.1 (*s,* Me$_2$*C*); 38.2 (*q*, Me$_2$N); 45.5 (*t*, CH_2); 56.8 (*s,* Me$_2$*C*); 71.8 (*t*, CH_2O); 169.4, 171.2, 173.2 (3*s,* 3 C=O). ESI-MS: 309 (100, $[M + Na]^+$]).

5.2. *3-[1-(*N,N-*Dimethylcarbamoyl)cyclopentylcarbamoyl]-2,2-dimethylpropyl Acetate* (**9c**). According to *GP 3* from **8a** (348 mg, 2 mmol) in dry THF (20 ml) and **10c** (290 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 20:1). Yield: 549 mg (88%) of **9c**. White powder. M.p. 139.0-140.2°. ^{1}H-NMR: 1.02 (*s,* Me$_2$C); 1.66-1.78, 1.83-1.93 (2*m,* 4 CH_2); 2.07 (*s,*

MeCO); 2.18-2.26 (*m,* CH_2); 2.98 (br. *s,* Me_2N); 3.96 (*s,* CH_2O); 6.41 (br. *s,* NH). ^{13}C-NMR: 21.0 (*q*, *Me*CO); 22.4 (*t*, CH_2); 24.6 (*q*, *Me*$_2$C); 34.3 (*t*, CH_2); 35.7 (*s,* Me_2C); 38.2 (*q*, Me_2N); 44.3 (*t*, CH_2); 66.8 (*s,* Me_2C); 71.9 (*t*, CH_2O); 169.8, 171.4, 172.5 (3*s,* 3 C=O). CI-MS: 313 (40, $[M + H]^+$), 268 (100, $[M - NMe_2]^+$),

5.3. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl Acetate* (**9d**). According to *GP 3* from **8a** (348 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 40:1). Yield: 584 mg (84%) of **9d**. White powder. M.p. 94.1-95.8°. ^{1}H-NMR: 0.99, 1.48 (2*s,* 2 Me_2C); 2.03 (*s,* MeCO); 2.12 (*s,* CH_2); 3.26 (*s,* MeN); 3.91 (*s,* CH_2O); 6.38 (*s,* NH); 7.21-7.43 (*m,* 5 arom. H). ^{13}C-NMR: 20.9 (*q*, *Me*CO); 24.4, 26.0 (2*q*, 2 *Me*$_2$C); 34.0 (*s,* Me_2C); 41.5 (*q*, MeN); 46.0 (*t*, CH_2); 58.3 (*s,* Me_2C); 71.7 (*t*, CH_2O); 127.9, 128.2, 129.3 (3*d,*5 arom. CH); 144.5 (*s,* arom. C); 169.6, 171.2, 173.4 (3*s,* 3 C=O). ESI-MS: 371 (100, $[M + Na]^+$]).

5.4. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2-phenylpropyl Acetate* (**9e**). According to *GP 3* from **8c** (444 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 50:1). Yield: 689 mg (87%) of **9e**. White powder. M.p. 133.3-134.2°. ^{1}H-NMR: 1.32, 1.38 (2*s,* Me_2C); 2.09 (*s,* MeCO); 2.18-2.25, 2.43-2.50 (2*m,* CH_2); 3.20-3.26 (*m,* MeN, CH); 3.72-3.77 (*m,* CH_2O); 5.97 (*s,* NH); 7.17-7.36 (*m,* 10 arom. H). ^{13}C-NMR: 21.1 (*q, Me*CO); 26.1, 26.2 (2*q*, *Me*$_2$C); 40.9 (*t*, CH_2); 41.3 (*q*, MeN); 44.5 (*d*, CH); 58.1 (*s,* Me_2C); 67.0 (*t*, CH_2O); 126.9, 127.5, 127.9, 128.6, 129.3 (5*d,* 5 arom. CH); 141.8, 144.4 (2*s,* 2 arom. C); 169.9, 171.0, 173.0 (3*s,* 3 C=O). ESI-MS: 419 (100, $[M + Na]^+$).

5.5. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2-methyl-2-phenylpropyl Acetate* (**9f).** According to *GP 3* from **8d** (472 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 50:1). Yield: 689 mg (84%) of **9f**.

White powder. M.p. 135.1-136.6°. ^{1}H-NMR: 1.08, 1.16, 1.36 (3*s,* Me, Me_2C); 2.08 (*s,* MeCO); 2.11-2.17 (*m,* CH_2); 3.16 (*s,* MeN); 4.21 (*s,* CH_2O); 5.64 (*s,* NH); 7.09-7.41 (*m,* 10 arom. H). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 22.4, 26.1, 26.6 (3*q*, Me, *Me*$_2$C); 30.8 (*s,* Me$_2$*C*); 41.1 (*q*, MeN); 46.3 (*t*, CH_2); 57.4 (*s,* Me$_2$*C*); 71.1 (*t*, CH_2O); 126.1, 127.6, 127.9, 128.5, 128.9, 129.3 (6*d,* 10 arom. CH); 143.6, 144.8 (2*s,* 2 arom. C); 168.9, 170.8, 172.9 (3*s,* 3 C=O). CI-MS: 411 (42, $[M + H]^+$), 304 (100, $[M - Me(Ph)N]^+$), 175 (21).

5.6. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2,2-dimethylbutyl Acetate* (**9g**). According to *GP 3* from **8e** (372 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 50:1). Yield: 637 mg (88%) of **9g.** White powder. M.p. 139.6-140.9°. ^{1}H-NMR: 0.99, 1.00 (2*s,* Me$_2$C); 1.05 (*d, J* = 3.9, *Me*CH); 1.40, 1.41 (2*s,* Me$_2$C); 2.05-2.12 (*m,* MeCO, CH); 3.19 (*s,* MeN); 3.86 (*q*, CH_2O); 6.66 (*s,* NH); 7.14-7.46 (*m,* 5 arom. H). ^{13}C-NMR: 12.2 (*q*, Me); 20.8 (*q*, *Me*CO); 21.6, 22.4, 24.8, 25.0 (4*q*, 2 *Me*$_2$C); 35.9 (*s,* Me$_2$*C*); 41.4 (*q*, MeN); 46.4 (*d*, CH); 58.5 (*s,* Me$_2$*C*); 71.3 (*t*, CH_2O); 128.0, 128.4, 129.3 (3*d,* 5 arom. CH); 144.1 (*s,* arom. C); 170.9, 172.7, 173.7 (3*s,* 3 C=O). ESI-MS: 385 (100, $[M + Na]^+$).

5.7. *3-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-2,2,3-trimethylbutyl Acetate* (**9h**). According to *GP 3* from **8f** (404 mg, 2 mmol) in dry THF (20 ml) and **10b** (365 mg, 2.1 mmol), CC (CH_2Cl_2/MeOH 50:1). Yield: 684 mg (91%) of **9h.** White powder. M.p. 119.9-120.9°. ^{1}H-NMR: 0.93, 1.11, 1.47 (3*s,* 3 Me$_2$C); 2.04 (*s,* MeCO); 3.26 (*s,* MeN); 3.98 (*s,* CH_2O); 7.04 (*s,* NH); 7.18-7.41 (*m,* 5 arom. H). ^{13}C-NMR: 21.0, 21.7, 24.9 (3*q*, 3 *Me*$_2$C); 38.6 (*s,* Me$_2$*C*); 41.7 (*q*, MeN); 47.2, 58.8 (2*s,* 2 Me$_2$*C*); 70.7 (*t*, CH_2O); 128.3, 128.6, 129.5 (3*d,* 5 arom. CH); 144.1 (*s,* arom. C); 171.1, 174.3, 176.9 (3*s,* 3 C=O). ESI-MS: 415 (20, $[M + K]^+$), 399 (100, $[M + Na]^+$), 377 (60, $[M + H]^+$). Anal. calc. for $C_{21}H_{32}N_2O_4$ (376.50): C 66.99, H 8.57, N 7.44; found: C 66.35, H 8.28, N 7.15.

6. *Deprotection of* **9** *to give Hydroxydiamides* **4.** *General Procedure 4 (GP 4).* The amides **9** were treated with 4 equiv. of LiOH in THF/H_2O 2:1 at r.t. for 4-12 h. Evaporation of the solvent *i.v.*, extraction of the residue with CH_2Cl_2, drying ($MgSO_4$), evaporation *i.v.* and washing with Et_2O yielded the hydroxydiamides **4** as white powders, which were used without further purification.

6.1. *4-Hydroxy-3,3-dimethyl*-N-*[1-methyl-1-(*N,N-*dimethylcarbamoyl)ethyl]butanamide* (**4a**). According to *GP 4* from **9a** (858 mg, 3 mmol), 4 h. Yield: 677 mg (93%) of **4a**. White powder. M.p. 138.6-139.9°. ^{1}H-NMR: 0.99, 1.64 (2*s,* Me_2C); 2.14 (*s,* CH_2); 3.12 (br. *s,* Me_2N); 3.91 (*s,* CH_2O); 7.02 (*s,* NH). ^{13}C-NMR: 24.6, 24.8 (2*q*, 2 *Me*$_2$C); 34.6 (*s,* Me$_2$*C*); 38.8 (*q*, Me_2N); 45.4 (*t*, CH_2); 56.8 (*s,* Me$_2$*C*); 71.3 (*t*, CH_2O); 171.4, 173.0 (2*s,* 2 C=O). CI-MS: 244 (32, $[M + H]^+$]), 201 (100, $[M - Me_2N]^+$]).

6.2. *4-Hydroxy*-N-*[1-methyl-1-(*N,N-*dimethylcarbamoyl)ethyl]butanamide* (**4b**). A soln. of sodium 4-hydroxy-butanate (1.0 g, 7.9 mmol) in H_2O (10 ml) was acidified with 3N HCl. Extraction with AcOEt (5 × 30 ml), drying ($MgSO_4$), evaporation of the solvent *i.v.* yielded 520 mg (63%) of 4-hydroxybutanoci acid as a viscous fluid, which was used without further purification. All spectra were in accordance with the data in [35]. 4-Hydroxybutanoic acid (600 mg, 5.77 mmol) was dissolved in dry THF (20 ml) and **10a** (711 mg, 6.35 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred overnight at r.t., the solvent evaporated *i.v.* and the residue purified by CC (CH_2Cl_2/MeOH 10:1). Yield: 1134 mg (90%) of **4b**. White solid. M.p. 124.6-125.3°. ^{1}H-NMR: 1.48 (*s,* Me_2C); 1.73-1.82 (*m,* CH_2); 2.08 (*t, J* = 6.2, CH_2); 3.26 (*s,* Me_2N); 3.65 (*t, J* = 6.2, CH_2O); 6.38 (*s,* NH); 7.24-7.32 (*m,* 5 arom. H). ^{13}C-NMR: 24.4 (*t*, CH_2); 26.0 (*q*, *Me*$_2$C); 41.5 (*q*, Me_2N); 46.0 (*t*, CH_2); 58.3 (*s,* Me$_2$*C*); 71.7 (*t*, CH_2O); 127.9, 128.2, 129.3 (3*d,* 5 arom.

CH); 144.5 (*s,* arom. C); 171.2, 173.4 (2*s,* 2 C=O). CI-MS: 279 (85, $[M + H]^+$), 172 (100, $[M - Me_2N]^+$).

6.3. *4-Hydroxy-3,3-dimethyl*-N-*[1-(*N,N-*dimethylcarbamoyl)cyclopentyl]butanamide* (**4c**). According to *GP 4* from **9c** (936 mg, 3 mmol), 6 h. Yield: 738 mg (91%) of **4c**. White powder. M.p. 138.4-139.9°. ^{1}H-NMR: 0.99 (*s,* Me_2C); 1.62-1.76, 1.84-2.02 (2*m,* 4 CH_2); 2.21-2.39 (*m,* CH_2); 3.03 (br. *s,* Me_2N); 3.38 (*s,* CH_2O); 6.61 (br. *s,* NH). ^{13}C-NMR: 24.4 (*t*, CH_2); 25.2 (*q*, *Me*$_2$C); 35.7 (*s,* Me$_2$*C*); 37.3 (*t*, CH_2); 37.9 (*q*, Me_2N); 46.4 (*t*, CH_2); 66.6 (*s,* C); 71.9 (*t*, CH_2O); 172.2, 172.7 (2*s,* 2 C=O). ESI-MS: 309 (10, $[M + K]^+$), 293 (100, $[M + Na]^+$).

6.4. *4-Hydroxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl) ethyl]butanamide* (**4d**). According to *GP 4*, from **9d** (1044 mg, 3 mmol), 6 h. Yield: 845 mg (92%) of **4d**. White powder. M.p. 138.4-139.9°. ^{1}H-NMR: 0.92, 1.44 (2*s,* 2 Me_2C); 2.13 (*s,* CH_2); 3.22 (*s,* MeN); 3.91 (*s,* CH_2O); 6.32 (*s,* NH); 7.16-7.41 (*m,* 5 arom. H). ^{13}C-NMR: 25.2, 26.0 (2*q*, 2 *Me*$_2$C); 35.6 (*s,* Me$_2$*C*); 41.3 (*q*, MeN); 47.2 (*t*, CH_2); 58.2 (*s,* Me$_2$*C*); 71.4 (*t*, CH_2O); 127.9, 128.2, 129.2 (3*d,* 5 arom. CH); 144.3 (*s,* arom. C); 171.6, 173.1 (2*s,* 2 C=O). ESI-MS: 345 (20, $[M + K]^+$), 329 (100, $[M + Na]^+$). Anal. calc. for $C_{17}H_{26}N_2O_3$ (306.41): C 66.64, H 8.55, N 9.14; found: C 66.36, H 8.49, N 8.97.

6.5. *4-Hydroxy*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-3-phenyl butanamide* (**4e**). According to *GP 4*, from **9e** (1188 mg, 3 mmol), 8 h. Yield: 934 mg (88%) of **4e**. White powder. M.p. 129.0-129.9°. ^{1}H-NMR: 1.28, 1.35 (2*s,* Me_2C); 2.11-2.21, 2.34-2.46 (2*m,* CH_2); 3.17 (br. *s,* MeN, CH); 3.64-3.79 (*m,* CH_2O); 5.96 (*s,* NH); 7.10-7.41 (*m,* 10 arom. H). ^{13}C-NMR: 26.1, 26.2 (2*q*, *Me*$_2$C); 40.9 (*q*, MeN); 41.2 (*t*, CH_2); 44.5 (*d*, CH); 58.2 (*s,* Me$_2$*C*); 67.1 (*t*, CH_2O); 126.8, 127.5, 127.9, 128.6, 129.3

(5*d,* 10 arom. CH); 141.7, 144.4 (2*s,* 2 arom. C); 171.1, 173.0 (2*s,* 2 C=O). CI-MS (i-butane): 355 (100, $[M + H]^+$).

6.6. *4-Hydroxy*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-3-methyl-3-phenylbutanamide* (**4f**). According to *GP 4* from **9f** (820 mg, 2 mmol), 12 h. Yield: 587 mg (90%) of **4f**. White powder. M.p. 121.9-123.3°. ^{1}H-NMR: 1.22, 1.23, 1.24 (3*s,* Me, Me_2C); 2.11-2.19, 2.31-2.38 (2*m,* CH_2); 3.15 (*s,* MeN); 3.51-3.59, 3.83-3.89 (2*m,* CH_2O); 5.84 (*s,* NH); 7.11-7.43 (*m,* 10 arom. H). ^{13}C-NMR: 23.6, 26.1, 26.2 (3*q*, Me, Me_2C); 41.4 (*q*, Me_2N); 42.7 (*s,* Me_2C); 47.4 (*t*, CH_2); 58.1 (*s,* Me_2C); 70.6 (*t*, CH_2O); 126.1, 126.5, 127.8, 128.5, 129.3 (5*d,* 10 arom. CH); 144.5, 145.5 (2*s,* 2 arom. C); 170.9, 173.0 (2*s,* 2 C=O). CI-MS (i-butane): 327 (80, $[M + H]^+$), 221 (100, $[M - Ph(Me)N]^+$).

6.7. *4-Hydroxy-2,3,3-trimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl) ethyl]butanamide* (**4g**). According to *GP 4* from **9g** (724 mg, 2 mmol), 4 h. Yield: 576 mg (90%) of **4g**. White powder. M.p. 124.2-126.3°. ^{1}H-NMR: 1.00 (*s,* Me_2C); 1.09 (*d, J* = 4.6, *Me*CH); 1.40, 1.42 (2*s,* Me_2C); 2.08 (*q*, *J* = 4.6, CH); 3.18 (*s,* MeN); 3.51-3.59 (*m,* CH_2O); 6.96 (*s,* NH); 7.12-7.42 (*m,* 5 arom. H). ^{13}C-NMR: 12.7 (*q*, Me); 23.4, 24.2, 25.0 (3*q*, 3 Me_2C); 37.6 (*s,* Me_2C); 41.7 (*q*, MeN); 49.9 (*d*, CH); 58.9 (*s,* Me_2C); 69.3 (*t*, CH_2O); 128.4, 128.6, 129.5 (3*d,* 5 arom. CH); 143.9 (*s,* arom. C); 173.8, 175.6 (2*s,* 2 C=O). ESI-MS: 343 (100, $[M + Na]^+$).

6.8. *4-Hydroxy-2,2,3,3-tetramethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-butanamide* (**4h**). According to *GP 4*, from **9h** (752 mg, 2 mmol), 4 h. Yield: 608 mg (91%) of **9h**. White powder. M.p. 129.9-131.3°. ^{1}H-NMR: 0.88, 1.15, 1.46 (3*s,* 3 Me_2C); 3.29 (*s,* MeN); 3.44 (*s,* CH_2O); 6.48 (*s,* NH); 7.23-7.42 (*m,* 5 arom. H). ^{13}C-NMR: 21.5, 21.9, 24.6 (3*q*, 3 Me_2C); 39.6 (*s,* Me_2C); 41.6 (*q*, MeN); 47.6, 58.9 (2*s,* 2 Me_2C); 70.7 (*t*,

CH_2O); 128.2, 128.4, 129.4 (3*d,* 5 arom. CH); 143.9 (*s,* arom. C); 173.9, 177.8 (2*s,* 2 C=O). ESI-MS: 357 (100, $[M + Na]^+$).

7. *Attempted Direct Amide Cyclizations of Amides* **4.** *General Procedure 5 (GP 5).* A suspension of **4** (0.5 mmol) in dry toluene (50 ml) was heated to 100° and HCl gas was bubbled through the suspension for 4-6 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca.* 20 min). The solvent was evaporated, the white residue was washed with CH_2Cl_2 (3 × 15 ml) and dried in *h.v.* to yield imino lactone hydrochlorides **12** as white powders.

General Procedure 6 (GP 6). A suspension of **4** was treated as in *GP 5.* The solvent was evaporated, and the oily residue was purified by CC to yield the ω-chloro acids **11**.

7.1. *2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoic Acid Hydrochloride* (**12a**). According to *GP 5* from **4d** (153 mg, 0.5 mmol). Yield: 101 mg (84%). M.p. 158.3-159.1°. IR: 3431*w,* 2938*s,* 2804*s,* 1735v*s,* 1678v*s,* 1529*s,* 1414*m,* 1319*m,* 1194*s,* 1166*s,* 1003*m,* 946*m,* 754*m*. ^{1}H-NMR ((D_6)DMSO): 1.15, 1.56 (2*s,* 2 Me_2C); 3.13 (*s,* CH_2); 4.56 (*s,* CH_2O); 13.2 (br. *s,* COOH). ^{13}C-NMR ((D_6)DMSO): 23.5, 24.1 (2*q*, 2 *Me*$_2$C); 38.0, 60.1 (*s,* Me$_2$*C*); 88.0 (*t*, CH_2O); 162.0 (C=N); 180.2 (*s,* C=O). CI-MS: 200 (100, $[M - Cl]^+$).

7.2. *2-[(3,4,4-Trimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoic Acid Hydrochloride* (**12g**). According to *GP 5* from **4g** (160 mg, 0. 5mmol). Yield: 78 mg (73%). M.p. 152.4-153.6°. IR: 3386*w,* 2986*s,* 2776*s,* 1739v*s,* 1671v*s,* 1514*m,* 1478*s,* 1240*m,* 1178*s,* 1165*s,* 997*s,* 773*m*. ^{1}H-NMR ((D_6)DMSO): 1.08 (*d, J* = 4.9, Me); 1.21, 1.48 (2*s,* 2 Me_2C); 2.18 (*q, J* = 4.9, CH); 4.42 (*s,* CH_2O); 10.0 (br. *s,* COOH). ^{13}C-NMR ((D_6)DMSO): 12.0 (*q,* Me); 21.1, 22.2 (2*q*, 2 *Me*$_2$C); 36.5 (*s,* Me$_2$*C*); 46.1 (*d*, CH); 58.2

(*s,* Me_2C); 87.2 (*t*, CH_2O); 163.1 (C=N); 178.0 (*s,* C=O). CI-MS (i-butane): 214 (100, [*M* - Cl]$^+$), 108 (25). Anal. calc. for $C_{11}H_{20}NO_3Cl$ (249.74): C 52.90, H 8.07, N 5.61; found C 50.55, H 7.87, N 5.25.

7.3. *2-[(3,3,4,4-Tetramethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoic Acid Hydrochloride* (**12h).** According to *GP 5* from **4h** (167 mg, 0.5 mmol). Yield: 79 mg (78%), M.p. 157.0-157.6°. IR: 3390*w,* 3024*s,* 2938*s,* 2778*s,* 1738v*s,* 1669v*s,* 1476*s,* 1400*s,* 1313*m,* 1178*s,* 998*m,* 880*m,* 772*m*. ^{1}H-NMR ((D_6)DMSO): 0.97, 1.26, 1.56 (3*s,* 3 Me_2C); 4.58 (*s,* CH_2O); 12.9 (br. *s,* COOH). ^{13}C-NMR ((D_6)DMSO): 21.6, 22.5, 26.1 (3*q*, 3 *Me*$_2$C); 42.8, 46.6, 60.7 (3*s,* 3 Me_2C); 86.8 (*t*, CH_2O); 168.1 (C=N); 183.2 (*s,* C=O). ESI-MS: 228 (100, [*M* + Na]$^+$).

7.4. *2-(4-Chloro-3,3-dimethylbutanoylamino)-2-methylpropanoic Acid* (**11a**). According to *GP 6* from **4a** (122 mg, 0.5 mmol) or from **4d** (153 mg, 0.5 mmol), CC (CH_2Cl_2/acetone 10:1). Yield: 57 mg (48%) of **11a** from **4a** and 62 mg (52%) from **4d**. White powder. M.p. 116.1-117.3°. IR: 3356v*s,* 2981*s,* 2605*m,* 1717v*s,* 1620v*s,* 1548v*s,* 1473*s,* 1393*s,* 1294*m,* 1221*s,* 1158*s,* 1023*m,* 895*m,* 791*s*. ^{1}H-NMR ((D_6)DMSO): 1.00, 1.31 (2*s,* 2 Me_2C); 2.09 (*s,* CH_2); 3.59 (*s,* CH_2Cl); 7.12 (br. *s,* NH); 12.9 (br. *s,* COOH). ^{13}C-NMR ((D_6)DMSO): 24.9, 25.8 (2*q*, 2 *Me*$_2$C); 36.6 (*s,* Me_2C); 44.9 (*t*, CH_2); 55.3 (*t*, CH_2Cl); 60.3 (*s,* Me_2C); 172.1, 181.1 (2*s,* 2 C=O). ESI-MS: 260 (32, [*M*(^{37}Cl) + Na]$^+$), 258 (100, [*M*(^{35}Cl) + Na]$^+$).

7.5. *2-(4-Chlorobutanoylamino)-2-methylpropanoic Acid* (**11b**). According to *GP 6* from **4b** (140 mg, 0.5 mmol), CC (CH_2Cl_2/acetone 10:1). Yield: 62 mg (66%) of **11b**. White solid. M.p. 111.9-113.1°. IR: 3318v*s,* 2988*s,* 1721v*s,* 1623*s,* 156*s,* 1467*s,* 1399*m,* 1230*m,* 1166*s,* 1050*w,* 945*w,* 787*m*. ^{1}H-NMR: 1.57 (*s,* Me_2C); 2.07-2.13 (*m,* CH_2); 2.37 (*t*, *J* = 6.1, CH_2); 3.61 (*t*, *J* = 6.1, CH_2Cl); 7.29 (br. *s,* NH). ^{13}C-NMR : 24.7 (*q*, *Me*$_2$C); 33.9 (*t*,

CH_2); 44.4 (*t,* CH); 55.6 (*t*, CH_2Cl); 59.6 (*s,* Me_2C); 171.8, 176.6 (2*s,* 2 C=O). CI-MS: 210 (10, $[M(^{37}Cl) + NH_4]^+$), 208 (25, $[M(^{35}Cl) + NH_4]^+$), 172 (100, $[M - Cl]^+$).

7.6. *1-[(4-Chloro-3,3-dimethylbutyl-1-oxo)amino]cyclopentanecarboxylic Acid* (**11c**). According to *GP 6* from **4c** (135 mg, 0.5 mmol), CC (CH_2Cl_2:acetone 10:1). Yield: 69 mg (53%) of **11c**. White powder. M.p. 113.2-114.7°. ^{1}H-NMR: 1.02, 1.09 (2*s,* Me_2C); 1.71-1.76, 1.94-2.02 (2*m,* 4 CH_2); 3.22 (*m,* CH_2); 3.63 (*m,* CH_2Cl); 7.47 (br. *s,* NH). ^{13}C-NMR: 24.8 (*t*, CH_2); 25.3 (*q*, *Me*$_2$C); 36.3 (*q,* Me_2C); 37.5, 44.7 (2*t,* 2 CH_2); 55.0 (*t*, CH_2Cl); 66.1 (*s,* Me_2C); 171.7, 176.4 (2*s,* 2 C=O). CI-MS: 264 (28, $[M(^{37}Cl) + H]^+$), 262 (72, $[M(^{35}Cl) + H]^+$), 226 (100, $[M - Cl]^+$).

7.7 *2-(4-Chloro-3-phenylbutanoylamino)-2-methylpropanoic Acid* (**11d**). According to *GP 6* from **4e** (184 mg, 0.5 mmol), CC (CH_2Cl_2/acetone 20:1). Yield: 51 mg (43%) of **11d**. White powder. M.p. 119.6-121.8° (decomp). IR: 3320*vs,* 2928*s,* 1722*vs,* 1626*vs,* 1606*s,* 1557*s,* 1496*s,* 1442*s,* 1315*s,* 1260*m,* 1170*s,* 1079*m,* 752*s,* 696*s*. ^{1}H-NMR: 1.36, 1.39 (2*s,* Me_2C); 2.53-2.60, 2.70-2.78 (*m,* CH_2); 3.48-3.52 (*m,* PhC*H*); 3.85-3.91 (*m,* CH_2Cl); 7.24-7.32 (*m,* 5 arom. H); 7.45 (br. *s,* NH); 12.3 (br. *s,* COOH). ^{13}C-NMR: 24.8, 25.3 (2*q*, 2 *Me*$_2$C); 40.2 (*t*, CH_2); 45.3 (*d,* CH); 55.3 (*t*, CH_2Cl); 59.6 (*s,* Me_2C); 127.6, 128.7, 129.0 (3*d,* 5 arom. CH); 142.3 (*s,* arom. C); 171.1, 179.1 (2*s,* 2 C=O). CI-MS: 286 (15, $[M(^{37}Cl) + H]^+$), 284 (39, $[M(^{35}Cl) + H]^+$), 248 (100, $[M - Cl]^+$).

8. *Synthesis of dipeptide esters. General Procedure 7 (GP 7).* A suspension of **4** (0.5 mmol) in a mixture of dry toluene (50 ml) and alcohol (5 ml) was heated to reflux and HCl gas was bubbled through the suspension for 6 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca.* 20 min). The solvent was evaporated, and the oily residue was purified by CC to yield the products as colorless oils.

General Procedure 8 (GP 8). To solid **12a** (117 mg, 0.5 mmol), a 0.5 M soln. of CH_2N_2 in Et_2O (1 ml, 0.5 mmol) was added dropwise at 0°. After the disappearance of the yellow color, another 1 ml of CH_2N_2 was added, the mixture allowed to warm up to r.t., stirred for 15 min, filtered, and the solvent evaporated *i.v.* The white solid **14a** was used without further purification.

8.1. *Methyl 2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoate* (**14a**). Accordig to *GP 7* from **4d** (153 mg, 0.5 mmol), 5 ml of MeOH, CC (CH_2Cl_2/acetone 20:1). Yield: 50 mg (43%) of **14a**. White solid. M.p. 88.6-89.8°. IR: 2961*s,* 2876*m,* 1736v*s,* 1706v*s,* 1567*s,* 1360*m,* 1271*s,* 1143*s,* 101*m,* 919*m,* 731*s*. ^{1}H-NMR ((D_6)DMSO): 1.05, 1.28 (2*s,* 2 Me_2C); 2.24 (*s,* CH_2); 3.56 (*s,* MeO); 3.83 (*s,* CH_2O). ^{13}C-NMR ((D_6)DMSO): 23.6, 25.8 (2*q*, *Me*$_2$C); 36.6 (*s,* Me$_2$*C*); 42.4 (*t*, CH_2); 50.1 (*q*, MeO); 58.9 (*s,* Me$_2$*C*); 80.3 (*t*, CH_2O); 162.2 (*s,* C=N); 175.3 (*s,* C=O). CI-MS: 231 (100, [*M* + NH_4]$^+$).

An experiment according to *GP 8* yielded 113 mg (98%) of **14a** as a white solid.

8.2. *Ethyl 2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methylpropanoate* (**14b).** According to *GP 7* from **4d** (153 mg, 0.5 mmol), 5 ml of EtOH, after CC (CH_2Cl_2/acetone 20:1). Yield: 49 mg (43%) of **14b** and 51 mg of *ethyl 2-(4-chloro-3,3-dimethylbutanoylamino)-2-methylpropanoate* **18b** (38%) as colorless oils.

14b: IR: 2965v*s,* 2893*s,* 1714v*s,* 1697v*s,* 1468*s,* 1380*s,* 1273*s,* 1166*s,* 1035*m,* 911*m,* 731*s*. ^{1}H-NMR: 1.11 (*s,* Me$_2$C); 1.21 (*t*, *J* = 7.1, *Me*CH_2); 1.43 (*s,* Me$_2$C); 2.33 (*s,* CH_2); 3.82 (*s,* CH_2O); 4.18 (*q*, *J* = 7.1, MeC*H*$_2$). ^{13}C-NMR: 14.3 (*q*, Me); 25.1, 26.6 (2*q*, *Me*$_2$C); 37.1 (*s,* Me$_2$*C*); 44.5 (*t*, CH_2); 60.4 (*t*, Me*C*H_2); 60.5 (*s,* Me$_2$*C*); 81.9 (*t*, CH_2O); 163.7 (*s,* C=N); 176.5 (*s,* C=O). ESI-MS: 477 (15, [2*M* + Na]$^+$), 250 (100, [*M* + Na]$^+$), 228 (12, [*M* + H]$^+$).

18b: ^{1}H-NMR: 1.05 (*s,* Me_2C); 1.16 (*t*, *J* = 7.2, *Me*CH_2); 1.27 (*s,* Me_2C); 2.24 (*s,* CH_2); 3.81 (*s,* CH_2Cl); 4.02 (*q*, *J* = 7.2, MeC*H*$_2$); 6.02 (br. *s,* NH). ^{13}C-NMR: 14.2 (*q*, Me); 24.7, 25.8 (2*q*, 2 *Me*$_2$C); 35.8 (*s,* Me_2C); 38.4 (*t,* CH_2); 54.9 (*t*, CH_2O); 61.3 (*t*, Me*C*H_2); 65.6 (*s,* Me_2C); 170.4, 172.6 (2*s,* 2 C=O). ESI-MS: 288 (31), 286 (100, $[M + Na]^+$).

8.3. *Methyl 2-Methyl-2-[(4-methyl-4-phenyltetrahydrofuran-2-yliden)amino]propanoate* (**14c**). According to *GP 7* from **4f** (168 mg, 0.5 mmol), 5 ml of MeOH, CC (CH_2Cl_2/acetone 25:1). Yield: 77 mg (56%) of **14c**. Colorless oil. ^{1}H-NMR: 1.45, 1.46, 1.49 (3*s,* Me, Me_2C) ; 2.73-2.79, 2.97-3.02 2 (2*m,* CH_2); 3.68 (*s,* MeO); 4.31 (*s,* CH_2O); 7.16-7.36 (*m,* 5 arom. H). ^{13}C-NMR: 26.1, 26.7, 27.1 (3*q*, Me, *Me*$_2$C); 43.0 (*t*, CH_2); 44.6 (*s,* Me_2C); 51.3 (*q*, MeO); 60.1 (*s,* Me_2C); 80.9 (*t*, CH_2O); 127.3, 126.8, 128.7 (3*d,* 5 arom. CH); 144.5 (*s,* arom. C); 163.0 (*s,* C=N); 176.7 (*s,* C=O). CI-MS: 276 (100, $[M + H]^+$), 108 (22).

8.4. *Ethyl 1-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]cyclopentanecarboxylate* (**14d**). According to *GP 7* from **4c** (135 mg, 0.5 mmol), 5 ml of EtOH, CC (CH_2Cl_2/acetone 20:1). Yield: 71 mg (28%) of **14d** and 45 mg (31%) of *ethyl 1-(4-chloro-3,3-dimethylbutanoylamino)cyclopentanecarboxylate* (**18d**) as colorless oils.

14d: ^{1}H-NMR: 1.12 (*s,* Me_2C); 1.21 (*t*, *J* = 7.0, *Me*CH_2); 1.81-1.94 (*m,* 4 CH_2); 2.41 (*s,* CH_2); 3.89 (*s,* CH_2O); 4.14 (*q*, *J* = 7.0, MeC*H*$_2$). ^{13}C-NMR: 14.3 (*q*, Me); 25.1 (*q*, *Me*$_2$C); 37.3, 37.6, 38.4, 39.1 (4*t,* 4 CH_2); 44.2 (*s,* Me_2C); 44.9, 47.1 (2*t,* 2 CH_2); 60.6 (*s,* Me_2C); 82.2 (*t*, CH_2O); 162.4 (*s,* C=N); 174.9 (*s,* C=O). CI-MS: 254 (100, $[M + H]^+$), 200 (18, $[M - Et]^+$), 158 (36).

18d: ^{1}H-NMR: 1.09 (*s,* Me_2C); 1.20 (*t*, *J* = 6.9, *Me*CH_2); 1.74-1.82, 1.84-1.94 (2*m,* 4 CH_2, Me_2C); 2.16 (*s,* CH_2); 3.56 (*s,* CH_2O); 4.16 (*q*, *J* = 6.9, MeC*H*$_2$); 6.02 (br. *s,* NH). ^{13}C-NMR: 14.2 (*q*, Me); 24.7, 25.8 (2*q*, 2 *Me*$_2$C); 35.8 (*s,* Me_2C); 37.4, 37.7, 38.4, 39.1

(4*t,* 4 CH_2); 44.2 (*t*, CH_2); 54.9 (*t*, CH_2O); 61.3 (*t*, Me*C*H_2); 65.6 (*s,* Me_2C); 170.4, 172.6 (2*s,* 2 C=O). CI-MS: 292 (34, [*M*(^{37}Cl) + H]$^+$), 290 (100, [*M*(^{35}Cl) + H]$^+$), 254 (28).

8.5. *Methyl 2-(4-Hydroxy-3,3-dimethylbutanoylamino)-2-methylpropanoate* (**17a**). According to *GP 7* from **9d** (174 mg, 0.5 mmol), 5 ml of MeOH, CC (CH_2Cl_2/acetone 20:1). Yield: 56 mg (48%) of **17a**. Colorless oil. ^{1}H-NMR: 0.98, 1.43 (2*s,* 2 Me_2C); 2.11 (*s,* CH_2); 3.29 (*s,* CH_2O); 3.78 (*s,* MeO); 6.25 (*s,* NH). ^{13}C-NMR: 24.6, 25.2 (2*q*, 2 *Me*$_2$C); 35.7 (*s,* Me_2C); 46.9 (*t*, CH_2); 52.5 (*q*, MeO); 56.4 (*s,* Me_2C); 71.2 (*t*, CH_2O); 171.9, 174.9 (2*s,* 2 C=O). ESI-MS: 254 (100, [*M* + Na]$^+$).

8.6. *Methyl 2-(4-Hydroxy-3-methyl-3-phenylbutyrylamino)-2-methylpropanoate* (**17b**). According to *GP G* from **9f** (205 mg, 0.5 mmol) with 5 ml MeOH, CC (CH2Cl2/acetone 20:1). Yield 57 mg (38%) of **17b**. Colorless oil. ^{1}H-NMR: 1.38 (*s,* Me_2C); 1.39 (*s,* Me); 2.47-2.51, 2.66-3.70 (2*m,* CH_2); 3.65-3.69, 3.89-3.92 (2*m,* CH_2O); 3.68 (*s,* MeO); 6.25 (*s,* NH); 7.19-7.42 (*m,* 5 arom. H). ^{13}C-NMR: 23.3, 24.5, 24.6 (3*q*, 3 Me); 43.0 (*t*, CH_2); 46.5 (*s,* C); 52.3 (*q*, MeO); 56.1 (*s, C*); 70.3 (*t*, CH_2O); 126.0, 126.4, 128.4 (3*d,* 5 arom. CH); 145.4 (*s,* arom. C); 171.2, 174.7 (2*s,* 2 C=O). CI-MS (i-butane): 294 (100, [*M* + H]$^+$).

9. *Protection of Hydroxy Amide* **4d**. 9.1. *4-Benzyloxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]butanamide* (**9g**). To a soln. of **4d** (1 mmol, 306 mg) in dry THF (20 ml), NaH (44 mg, 1.1 mmol, 60% suspension in mineral oil) was added at 0°. After 1 h at r.t., benzylbromide (171 mg, 1 mmol) was added and the mixture heated to reflux for 3 h. Washing with brine, extraction with Et_2O, drying ($MgSO_4$) and evaporation *i.v.* yielded a colorless oil, which was purified by CC (CH_2Cl_2/acetone 40:1). Yield: 329 mg (73%) of **9g**. Colorless oil. ^{1}H-NMR: 0.99, 1.36 (2*s,* 2 Me_2C); 2.18 (*s,* CH_2); 3.12 (*s,* CH_2O); 3.22 (*s,* MeN); 4.43 (*s,* PhC*H*$_2$); 5.91 (br. *s,* NH); 7.12-7.43 (*m,* 10

arom. H). ^{13}C-NMR: 25.4, 26.7 (2*q*, 2 *M*e$_2$C); 34.8 (*s,* Me$_2$*C*); 41.3 (*q*, MeN); 46.3 (*t*, CH_2); 57.7 (*s,* Me$_2$*C*); 73.1 (*t*, CH_2O); 78.5 (*t*, Ph*C*H$_2$); 127.4, 127.6, 127.7, 127.8, 128.3, 129.2 (6*d*, 10 arom. CH); 138.4, 145.0 (2*s,* 2 arom. C); 170.6, 173.2 (2*s,* 2 C=O). CI-MS (i-butane): 397 (100, $[M + H]^+$).

9.2. *{2,2-Dimethyl-3-[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl]-propyl}[(9*H*-fluoren-9-yl)methyl] Carbonate* (**9h**). To a soln. of **4d** (306 mg, 1 mmol) in CH_2Cl_2 (20 ml), pyridine (3 ml) and FmocCl (284 mg, 1.1 mmol) were added. The mixture was stirred at r.t. for 3 h, diluted with CH_2Cl_2 (30 ml), washed with a 10% $CuSO_4$ soln. and brine, the org. fractions were dried ($MgSO_4$) and evaporated *i.v.* and purified by CC (CH_2Cl_2/acetone 30:1). Yiled: 450 mg (88%) of **9h**. White powder. M.p. 108.9-110.6°. IR: 3320v*s,* 2966*s,* 1745v*s,* 1678v*s,* 1650v*s,* 1599*s,* 1532*s,* 1441*s,* 1386*s,* 1316*m,* 1154*m,* 964*m,* 909*s,* 758*m*. ^{1}H-NMR: 0.99, 1.39 (2*s,* 2 Me$_2$C); 1.86 (*s,* CH_2); 3.19 (*s,* MeN); 3.92 (*s,* CH_2O); 1.15 (*t, J* = 5.8, CH_2CH); 4.36 (*d, J* = 5.8, C*H*$_2$CH); 6.12 (*s,* NH); 7.09-7.32, 7.50-7.80 (2*m,* 13 arom. H). ^{13}C-NMR: 24.5, 25.5 (2*q*, 2 *Me*$_2$C); 34.2 (*s,* Me$_2$*C*); 41.3 (*q*, MeN); 45.3 (*t*, CH_2); 58.0 (*s,* Me$_2$*C*); 69.7 (*t*, CH_2O); 75.1 (*t*, *C*H$_2$CH); 119.9 (*d*, CH); 125.0, 127.0, 127.7, 127.8, 127.9, 129.1 (6*d,* 13 arom. CH); 141.2, 143.3, 144.5 (3*s,* 5 arom. C); 155.2 (*s,* NC(O)O); 169.4, 173.1 (2*s,* 2 C=O). ESI-MS: 551 (100, $[M + Na]^+$).

9.3. *4-(Benzyloxy)methoxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)-ethyl]butanamide* (**9i**). To a soln. of **4d** (306 mg, 1 mmol) in CH_2Cl_2 (20 ml) was added (i-Pr)$_2$NEt (142 mg, 1.1 mmol) and benzyloxymethylchloride (BomCl, 156 mg, 1 mmol). The mixture was stirred at r.t. for 12 h, diluted with CH_2Cl_2 (30 ml), washed with NH_4Cl soln. and brine, dried ($MgSO_4$), evaporated *i.v.* and purified by CC (CH_2Cl_2/acetone 40:1). Yield: 375 mg (88%) **9i**. Colorless oil. ^{1}H-NMR: 0.99, 1.42 (2*s,* 2 Me$_2$C); 1.84 (*s,*

CH_2); 3.22 (*s,* MeN); 3.32 (*s,* CH_2); 4.51, 4.68 (2*s,* CH_2); 5.94 (br. *s,* NH); 7.08-7.42 (*m,* 10 arom. H). ^{13}C-NMR: 25.0, 26.3 (2*q*, 2 *Me*$_2$C); 34.5 (*s,* Me$_2$*C*); 41.2 (*q*, MeN); 45.9 (*t*, CH_2); 57.8 (*s,* Me$_2$*C*); 69.3, 76.2, 94.8 (3*t*, 3 CH_2); 127.6, 127.7, 127.8, 128.3, 129.0, 129.2 (6*d*, 10 arom. CH); 137.6, 144.6 (2*s,* 2 arom. C); 170.2, 173.1 (2*s,* 2 C=O). CI-MS: 427 (16, $[M + H]^+$), 320 (100, $[M - Ph(Me)N]^+$), 108 (16).

10. *Synthesis of 1,3-Oxazol-5(4*H*)-ones.* 10.1. *3-(4,4-Dimethyl-1,3-oxazol-5(4*H*)-on-2-yl)-2,2-dimethylpropyl Acetate* (**16a**)**.** According to *GP 6* from **9d** (153 mg, 0.5 mmol), 4 min HCl gas, CC (CH_2Cl_2/acetone 40:1). Yield: 123 mg (51%) of **16a**. White solid. M.p. 99.5-101.7°. Recovered starting material: 33 mg (21%). IR: 3385*m,* 2976*s,* 2937*s,* 1820v*s,* 1739v*s,* 1672v*s,* 1525*m,* 1474*s,* 1379*s,* 1240v*s,* 1072*s,* 1041*s,* 966*s,* 897*m*. ^{1}H-NMR: 1.05, 1.36 (2*s,* 2 Me$_2$C); 2.04 (*s,* MeCO); 2.42 (*s,* CH_2); 3.92 (*s,* CH_2O), 7.21-7.34 (*m,* 5 arom. H). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 24.4, 24.6 (2*q*, 2 *Me*$_2$C); 34.3 (*s,* Me$_2$*C*); 38.0 (*t*, CH_2); 65.3 (*s,* Me$_2$*C*); 71.6 (*t*, CH_2O); 161.9 (*s,* C=N); 170.9, 181.4 (2*s,* 2 C=O). ESI-MS: 541 (100, $[2(M + H_2O) + Na]^+$), 371 (25), 282 (70, $[M + H_2O + Na]^+$).

10.2. *2-(3-Benzyloxy-2,2-dimethylpropyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one* (**16b**). According to *GP 6*, from **9g** (198 mg, 0.5 mmol), 4 min HCl gas, CC (CH_2Cl_2/acetone 50:1). Yield: 49 mg (34%) of **16b**. White powder. M.p. 104.2-106.0°. Recovered starting material: 124 mg (31%). IR: 2951*s,* 1894*s,* 2565*w,*1822v*s,* 1723v*s,* 1612v*s,* 1534v*s,* 1458*s,* 1265*s,* 1101*s,* 1058*m,* 1040*m,* 911*m*. ^{1}H-NMR: 1.01, 1.38 (2*s,* 2 Me$_2$C); 2.48 (*s,* CH_2); 3.14 (*s,* CH_2O); 4.56 (*s,* PhC*H*$_2$); 7.21-7.34 (*m,* 5 arom. H). ^{13}C-NMR: 24.5, 24.9 (2*q*, 2 *Me*$_2$C); 35.4 (*s,* Me$_2$*C*); 38.3 (*t*, CH_2); 65.2 (*s,* Me$_2$*C*); 73.3 (*t*, CH_2O); 78.6 (*t*, Ph*C*H$_2$); 127.5, 128.1, 128.3 (3*d*, 5 arom. CH); 138.5 (*s,* arom. C); 162.5 (*s,* C=N); 182.1 (*s,* C=O). CI-MS (i-butane): 290 (18, $[M + H]^+$), 200 (100, $[M - Bn]^+$).

10.3. *[3-(4,4-Dimethyl-1,3-oxazol-5(4*H*)-on-2-yl)-2,2-dimethylpropyl][(9*H*-fluoren-9-yl)methyl] Carbonate* (**16c**). According to *GP 6* from **9h** (169 mg, 0.33 mmol), 4 min HCl gas, CC (CH_2Cl_2/acetone 80:1). Yield: 64 mg (46%) of **16c**. White powder. M.p. 93.8-95.2°. Recovered starting material: 66 mg (39%). IR: 3320*s,* 2966*s,* 1821v*s,* 1745v*s*, 1678v*s,* 1650v*s,* 1599*s,* 1532*s,* 1441*s,* 1386*m,* 1316*m,* 1156*m,* 909*s*. ^{1}H-NMR: 1.01, 1.34 (2*s,* 2 Me_2C); 2.32 (*s,* CH_2); 3.87 (*s,* CH_2O); 4.12 (*t, J* = 6.0, CH_2CH); 4.38 (*d, J* = 6.0, CH_2CH); 7.18-7.37, 7.53-7.81 (2*m,* 8 arom. H). ^{13}C-NMR: 24.3, 24.8 (2*q*, 2 Me_2C); 34.5 (*s,* Me_2C); 37.9, 46.7 (2*t*, 2 CH_2); 65.1 (*s,* Me_2C); 65.9 (*t*, CH_2O); 69.8 (*t*, CH_2CH); 119.9 (*d*, CH); 125.0, 126.8, 127.1, 127.7 (4*d,* 8 arom. CH); 141.2, 143.3 (2*s,* 2 arom. C); 155.0 (*s,* NC(O)O); 161.6 (*s,* C=N); 181.1 (*s,* C=O). CI-MS: 422 (16, $[M + H]^+$), 200 (100, $[M$ - Fmoc$]^+$), 179 (44).

10.4. *2-[3-(Benzyloxy)methoxy-2,2-dimethylpropyl]-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (***16d***)*. According to *GP 6* from **9i** (143 mg, 0.33 mmol), 5 min HCl gas, CC (CH_2Cl_2/acetone 60:1). Yield: 42 mg (36%). White solid. M.p. 104.1-105.8°. Recovered starting material: 52 mg (35%). ^{1}H-NMR: 0.97, 1.36 (2*s,* 2 Me_2C); 2.42, 3.36, 4.59, 4.73 (4*s,* 4 CH_2); 7.14-7.43 (*m,* 5 arom. H). ^{13}C-NMR: 24.4, 24.7 (2*q*, 2 Me_2C); 34.9 (*s,* Me_2C); 45.5 (*t*, CH_2); 56.8 (*s,* Me_2C); 69.3, 76.1, 94.8 (3*t*, 3 CH_2); 127.7, 128.3, 129.5 (3*d*, 5 arom. CH); 137.6 (*s,* arom. C); 162.4 (*s,* C=N); 172.6 (*s,* C=O). CI-MS (i-butane): 320 (100, $[M + H]^+$).

10.5. *2,2-Dimethyl-3-(4-oxo-3-oxa-1-azaspiro[4.4]non-1-en-2-yl)propyl Acetate* (**16e**). According to *GP 6* from **9c** (156 mg, 0.5 mmol), 5 min HCl gas, CC (CH_2Cl_2/acetone 30:1). Yield: 45 mg (34%) of **16e**. White solid. M.p. 101.1-103.1°. Recovered starting material: 33 mg (21%). IR: 3385*w,* 2976*s,* 2937*s,* 1820v*s,* 1739v*s,* 1672v*s,* 1474*m,* 1379*s,* 1240*s,* 1072*s,* 1041*s,* 966*m*. ^{1}H-NMR: 1.01 (*s,* Me_2C); 1.73-2.04 (*m,* MeCO, 4

CH_2); 2.42 (*s,* CH_2); 3.90 (*s,* CH_2O). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 24.5 (*q*, *Me*$_2$C); 25.8 (*t*, 2 CH_2); 34.3 (*s,* Me$_2$*C*); 38.0, 38.2 (2*t*, 3 CH_2); 71.6 (*t*, CH_2O); 73.9 (*s,* spiro-C); 161.8 (*s,* C=N); 170.9, 182.1 (2*s,* 2 C=O). ESI-MS: 593 (100, $[2M + H_2O + Na]^+$), 324 (58, $[M + H_2O + K]^+$), 308 (64, $[M + H_2O + Na]^+$), 286 (90, $[M + H_2O + H]^+$).

11. *2-[(4,4-Dimethyltetrahydrofuran-2-yliden)amino]-2-methyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]propanamide* (**15**). To solid **12a** (100 mg, 0.42 mmol) a soln. of **10b** (110 mg, 3 mmol, 1.5 equiv.) in CH_2Cl_2 (5 ml) was added under vigorous stirring. The solvent was immediately removed *i.v.* and the suspension left at r.t. overnight. CC (CH_2Cl_2/acetone 20:1) yielded 102 mg (64%) of **15**. White powder. M.p. 142.1-143.3°. IR: 3364v*s,* 2976*s,* 2937*s,* 1708v*s,* 1666v*s,* 1645v*s,* 1493*s,* 1380*s,* 1223*m,* 1111*m,* 1014*s,* 781*m,* 710*s*. ^{1}H-NMR: 1.08, 1.42, 1.50 (3*s,* 3 Me$_2$C); 2.26 (*s,* CH_2); 3.21 (*s,* MeN); 3.89 (*s,* CH_2O); 7.06-7.29 (*m,* 5 arom. H); 8.07 (br. *s,* NH). ^{13}C-NMR: 23.8, 24.9, 26.1 (3*q*, 3 *Me*$_2$C); 36.5 (*s,* Me$_2$*C*); 41.0 (*q,* MeN); 45.2 (*t,* CH_2); 57.3, 60.6 (2*q*, 2 Me$_2$*C*); 81.5 (*t*, CH_2O); 127.3, 128.1, 129.4 (3*d*, 5 arom. CH); 144.8 (*s,* arom. C); 161.5 (*s,* C=N); 173.6, 176.3 (2*s,* 2 C=O). ESI-MS: 369 (100, $[M + Na]^+$).

12. *Methyl 2-(4-Hydroxy-3,3-dimethyl-2-oxobutylamino)-2-methylpropanoate* (**19**). To a soln. of 1-bromo-4-hydroxy-3,3-dimethylbutan-2-one (390 mg, 2 mmol) in Et_3N (5 ml), methyl 1-amino-2-methylpropanoate hydrochloride (456 mg, 3 mmol) was added. The mixture was heated under reflux overnight, cooled, diluted with CH_2Cl_2 (150 ml) and washed with a 10% $CuSO_4$ soln. and brine. Drying ($MgSO_4$), evaporation of the solvent and CC (CH_2Cl_2/acetone 30:1) yielded 195 mg (42%) of **19.** Yellow oil. IR: 2973*m,* 2884*m,* 1725v*s,* 1660v*s,* 1528*m,* 1471*s,* 1364*s,* 1192*s,* 1046*m*. ^{1}H-NMR: 1.12, 1.46 (2*s,* 2

Me_2C); 3.50, 3.54 (2*s,* 2 CH_2); 3.71 (*s,* MeO); 6.74 (br. *s,* NH). ^{13}C-NMR: 21.1, 25.1 (2*q*, 2 *Me*$_2$C); 48.4 (*s,* Me$_2$*C*); 49.9 (*t*, CH_2); 51.9 (*q*, MeO); 58.2 (*s,* Me$_2$*C*); 69.4 (*t*, CH_2O); 176.4, 212.6 (2*s,* 2 C=O). CI-MS (i-butane): 232 (70, $[M + H]^+$), 146 (100), 128 (40).

13. *X-ray Crystal-Structure Determination of* **11a, 11b, 12g, 12h** *and* **15** (*Table* and *Figs. 2-4*)[6]. All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [36] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table* and views of the molecules are shown in *Figs. 2-4.* Data reduction was performed with *HKL Denzo* and *Scalepack* [37]. The intensities were corrected for *Lorenz* and polarization effects and, in the cases of **11a, 12g** and **12h**, an absorption correction based on the multi-scan method [38] was applied. Each structure was solved by direct methods using SIR92 [39], which revealed the positions of all non-H atoms. The non-H atoms were refined anisotropically.

In the case of **11b,** there are two independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON* [40] but none could be found. Each molecule is disordered over two conformations. Two positions were defined for each atom of the Cl-$(CH_2)_3$- section of each molecule, except for the Cl-substituted C-atom, which is common to both conformations. Bond length restraints were applied to all bonds involving disordered atoms so as to maintain reasonable geometry. The best results

[6] CCDC- 286035 - 286040 contain supplementary crystallographic data for this paper. These data can be obtained free of charge form the *Cambridge Crystallographic Data Centre, via* http://www.ccdc.cam.ac.uk/data_request/cif

were obtained with relative site occupation factors of 0.65:0.35 and 0.80:0.20 for the disordered components of molecules A and B, respectively.

The hydroxy and ammonium H-atoms in **12g** and **12h**, as well as the amide H-atom in **15** and the amide and hydroxy H-atoms in **11a** and **11b** were placed in the positions indicated by difference electron density maps and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in all structures were placed in geometrically calculated positions and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the Me groups). The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. Corrections for secondary extinction were applied, except in the cases of **11a** and **11b**. Neutral atom scattering factors for non-H atoms were taken form [41] and the scattering factors for H-atoms were taken from [42]. Anomalous dispersion effects were included in F_c [43]; the values for f' and f'' were those of [44]. The values of the mass attenuation coefficients are those of [45]. All calculations were performed using the *SHELXL97* program [46]

Table 2. *Crystallographic Data of Compounds* **11a, 11b, 12g, 12h** and **15**

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